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Sleep Disorders

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Abstract Disturbances of sleep are commonly seen in many of the DSM-IV Axis I psychiatric disorders. Furthermore, psychiatric symptoms are commonly experienced in association with sleep disorders. This chapter reviews some basic physiology of sleep-wake regulation as well as the most common sleep disorders of importance to the practicing psychiatrist. Included are insomnia, restless legs syndrome, obstructive sleep apnea, narcolepsy, idiopathic and other hypersomnias, and parasomnias such as sleepwalking/sleep terrors and rapid eye movement (REM) sleep behavior disorder. In each case, diagnostic criteria are described, based both on the American Psychiatric Association *Diagnostic and Statistical Manual*, 4th edition, text revision (DSM-IV-TR) and the *International Classification of Sleep Disorders*, 2nd edition (ICSD-2). Discussions of epidemiology, clinical features, typical case examples, laboratory findings, course, differential diagnosis, etiology, and treatment considerations will enable the reader to recognize these disorders in their patients and to facilitate their treatment.

Keywords Hypersomnia · Insomnia · Narcolepsy · Obstructive sleep apnea · Parasomnias · REM-sleep behavior disorder · Restless legs syndrome · Sleep · Sleepwalking

1. Introduction

Terrestrial life has evolved in an environment of alternating periods of light and darkness. All mammalian species have developed corresponding alternations of rest and activity periods synchronous with the light–dark cycle. During periods of rest, basic changes in physiological and behavioral state are recognized as essential to maintenance of health and survival. By virtue of its importance for preservation of subsequently sustained wakeful attention, it enables vigilance, nutrition, reproduction, and protection against external threats. Furthermore, advances in recent years have demonstrated the importance of sleep for maintenance of metabolic functions, including normal glucose homeostasis and preserving the integrity of vascular and other tissues.

Sleep and its disturbances are important factors influencing the predisposition, precipitation, perpetuation, and manifestations of psychiatric disorders. An inspection of the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision (DSM-IV-TR) (1), reveals the presence of sleep symptoms as diagnostic criteria in major depressive episode and disorder, manic and hypomanic episodes, bipolar disorders, dysthymic disorder, cyclothymic disorder, posttraumatic stress disorder (PTSD), acute stress disorder, and generalized anxiety disorder. Indeed, the nightmares of PTSD have been granted "hallmark" significance (2). Additionally, panic disorder may emerge from the sleeping state, dissociative disorders may mimic sleep terrors, and sleep is often perturbed in disorders of substance abuse, dependence, and withdrawal. Disturbed sleep seems to be predictive of subsequent development or relapse of alcohol dependence and depression. Persisting short time latencies between sleep onset and the first rapid eye movement (REM) period, as well as diminished low frequency sleep–electroencephalogram (EEG) activity, have been demonstrated to predict recurrence of major depression (3, 4). This mood disorder is commonly comorbid in patients with insomnia, which may increase the risk of suicide and decrease responsiveness to cognitive–behavior therapy (CBT). Furthermore, insomnia may precipitate or worsen manic episodes in bipolar disorder (5–7).

Cognition and learning have been clearly demonstrated to benefit from sleep. Specifically, it seems that the consolidation of some forms of procedural learning and declarative memory are facilitated by sleep. Certainly, the maintenance of sustained attention during wakefulness is directly related to adequate previous nocturnal sleep (8, 9). In view of its effects on human consciousness, sleep is clearly "of the brain, by the brain, and for the brain" (10).

From: S. H. Fatemi and P. J. Clayton (eds.): *The Medical Basis of Psychiatry*

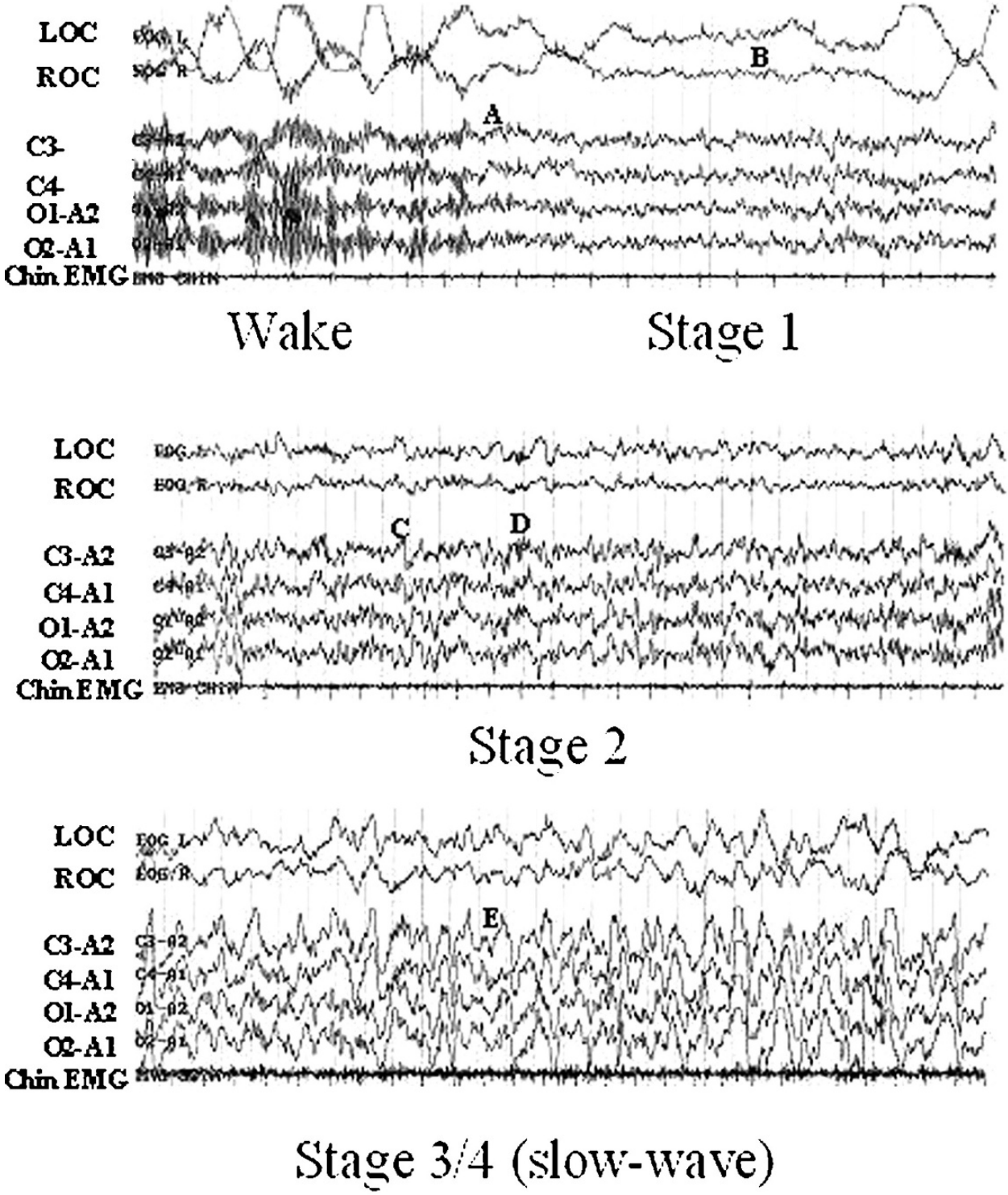

FIGURE 37.1. Polysomnographic patterns characteristic of wakefulness and sleep. Note the disappearance of the wakeful alpha rhythm with slower, relatively low-voltage EEG activity (*A*) and the appearance of slow, rolling eye movements (*B*) indicative of the transition from wakefulness to stage 1 sleep. Subsequently, the presence of biphasic K-complexes (*C*) and 12- to 14-Hz bursts of spindle activity (*D*) are associated with stage 2 sleep. This is followed by higher voltage, slow (2-Hz) EEG waves (*E*) characteristic of stages 3/4 or "slow wave sleep."

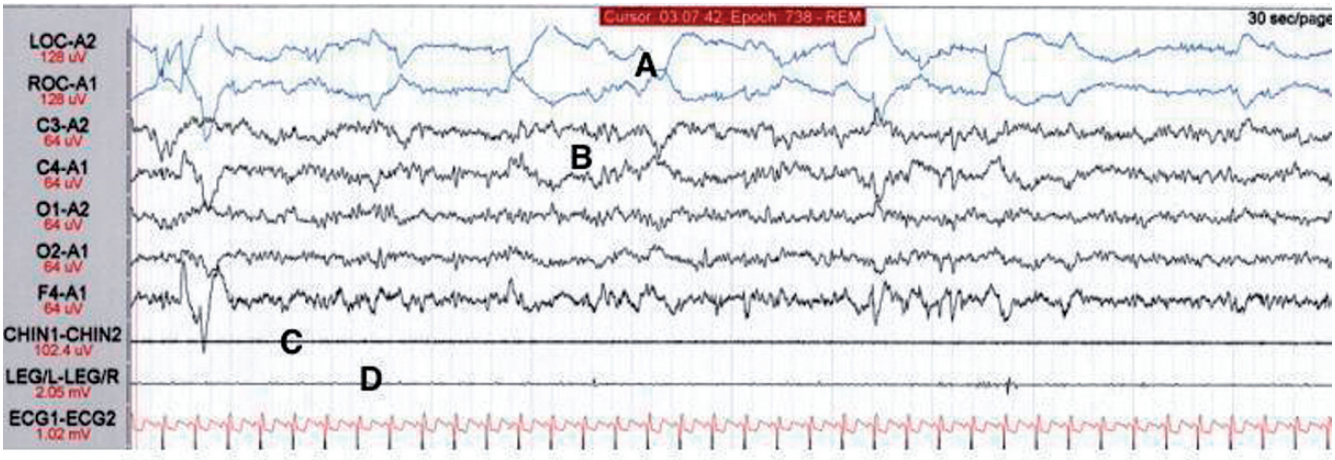

FIGURE 37.2. A 30-second epoch of REM sleep is exemplified by rapid eye movements (*A*), desynchronized low voltage mixed frequency EEG with occasional saw-tooth wave forms (*B*), absent muscle tone in the chin EMG (*C*), and no movement of lower extremities (*D*) (*see* Color Plate 9, following p. 650).

Physiological manifestations of sleep are measured clinically by polysomnography (PSG), with monitoring of brain electrical activity (EEG), eye movements (electrooculogram [EOG]), and peripheral muscle tone (electromyography [EMG]). These three parameters (supplemented with additional channels when applied clinically) permit distinctions between states of wakefulness and sleep. Since the discovery of REM sleep by Kleitman, Aserinsky, and Dement at the University of Chicago in 1953, these measurements have also characterized the difference between that distinct physiological state and the other stages of (non-REM) sleep. Since 1968, these have been defined by established conventions used to score each 30-second period, or epoch, of a recording (11). The transition from wakefulness to sleep is marked by a shift of EEG rhythm to a relatively low voltage, mixed but slower than wakeful frequency activity typically accompanied by some slow, rolling eye movements, characterizing a transitional stage 1 of non-REM sleep. Soon thereafter, the EEG includes intermittent bursts of 12 to 14 Hz activity, known as sleep spindles, representing thalamocortical interaction associated with decreases of cortical response to peripheral stimuli. Spindles and occasional biphasic waves of 0.5-second duration known as K-complexes define non-REM stage 2 sleep, which progresses variably to a pattern of slower, 2-Hz EEG activity that designates stage 3 ($\geq$20% of the 30-second epoch) and stage 4 ($\geq$50% of the epoch). These two stages are generally combined and referred to as slow-wave sleep. A revised scoring manual now designates stages of non-REM sleep as N1, N2, and N3 (378). Because such slower EEG frequencies reflect more synchronous cortical neuronal synaptic activity, these non-REM sleep stages have been called synchronized sleep, as distinguished from the low-voltage, faster-frequency, desynchronized activity of wakefulness. After approximately 90 minutes of non-REM sleep, there is typically a period of marked reduction of peripheral muscle tone on EMG, with lower-voltage (desynchronized) EEG, and intermittent bursts of rapid eye movements, defining the stage of REM sleep. This stage also represents a distinct physiological and behavioral state by virtue of continuous muscle atonia (except for occasional fasciculations or twitches), increased cerebral glucose metabolism, genital arousal, variations in cardiorespiratory rhythms, and vivid dreaming. After a variable period of minutes, there is resumption of non-REM sleep before the next periods of REM, which recur with a periodicity of approximately 90 minutes. Each successive REM period is longer in duration with a tendency for more frequent eye movements (Figs. 37.1 and 37.2 and Color Plate 9, following p. 650).

2. Basic Sleep–Wake Regulation

The regulation of sleep–wake transitions is complex and reflected throughout the neuraxis. As a result of his studies of viral encephalitis lethargica, known in the early twentieth century as "sleeping sickness," Baron Constantin von Economo stimulated the understanding of brain regions mediating this regulation and, by extension, dysregulation. Lesions at the junction of the brainstem and forebrain were associated with periods of prolonged sleepiness, whereas lesions of the anterior hypothalamus caused prolonged insomnia (12). By mid-century, Moruzzi and Magoun described the reticular activating system from the rostral pons through the midbrain reticular system (13). Interruption of this ascending influence was the cause of the hypersomnia observed by von Economo. Toward late century, two basic inputs to this arousal system were characterized. One is a pathway from cholinergic cells of the pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei of the pons that project to thalamic relay nuclei and the reticular nucleus of the thalamus, which is involved in gating of information flow to the cortex. These

pontine cholinergic cell groups fire actively during wakefulness as well as REM, but not during non-REM sleep. A second pathway influencing arousal begins with the noradrenergic neurons of the locus ceruleus (LC), serotonergic cells of the dorsal and medial raphe, dopaminergic cells of the periaqueductal grey matter, histaminergic cells of the tuberomammillary nucleus, and peptidergic neurons in the lateral hypothalamus. This multisource pathway extends to the lateral hypothalamic and basal forebrain areas, then on to the cortex. These monoaminergic neurons fire at their fastest rates during wakefulness, slow during non-REM sleep, and turn off during REM sleep. By the end of the century, the ventrolateral preoptic nucleus (VLPO) of the anterior hypothalamus was identified as a major inhibitory influence on the arousal system, with projections to all major components of this system in the hypothalamus and brainstem. VLPO neurons contain galanin and gamma-aminobutyric acid (GABA), both inhibitory neurotransmitters, and are innervated in return by the monoaminergic nuclei to constitute a feedback loop. The VLPO, including core and extended areas of cells, participates in the complex coordination of neuronal regulation of transitions between the states of wakefulness, non-REM sleep, and REM sleep. This complexity is governed by two influences, known as the homeostatic and circadian processes, which facilitate timing of the basic sleep–wake cycle. The homeostatic regulation of sleep (process S) constitutes the buildup of sleep need, or propensity, generated by previous wakefulness. It can be measured by the buildup of adenosine, which influences the VLPO, and also retrospectively by the intensity of slow-wave EEG activity that increases in non-REM sleep proportional to the duration of previous wakefulness. The second important regulatory influence is the circadian system (process C) which produces a fluctuating wake signal originating in the suprachiasmatic nucleus (SCN) of the hypothalamus. This is the primary clock that increases and decreases its signal on a nearly 24-hour periodicity. All is well when the homeostatic drive is maximal while the circadian wake signal decreases, and both processes are synchronized to the desired bedtime (14) (Figs. 37.3 and Color Plate 10, following p. 650).

A basic theme for the understanding of all sleep disorders is that errors of sleep–wake state regulation result in dissociated and recombined elements of wakefulness and sleep that create the clinical pictures constituting insomnia; excessive daytime sleepiness; dissociated REM-sleep components such as cataplexy, visual imagery, and sleep paralysis; and parasomnias such as sleepwalking, sleep terrors, and the dream enactment of REM-sleep behavior disorder. The most compelling consequence of disruption of sleep duration or continuity is the corresponding increase of homeostatic sleep drive that can override the wake state and create unsustained attention, automatic behavior, and unwanted onset of frank sleep.

Thereby, sleep disorders present concerns of profound relevance to psychiatry. In many cases, they must be distinguished from primary psychiatric disorders. Conversely, primary insomnia, obstructive sleep apnea (OSA), narcolepsy, and certainly parasomnias may be misdiagnosed and inappropriately treated as psychiatric disorders, especially if the symptoms are particularly bizarre or violent, with emotional, cognitive, and/or perceptual aberrations. Most sleep disorders can be precipitated or worsened by stress as well as cause considerable distress and dysfunction in their own right. Sleep symptoms may be the presenting complaints in cases of other medical and neurological disorders that might come first to the attention of a psychiatrist.

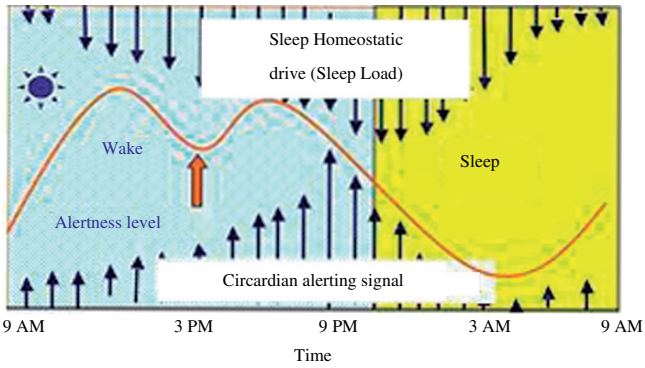

FIGURE 37.3. The two-process model of sleep–wake regulation. With ongoing wakefulness, the homeostatic sleep drive (process S) increases, reaching its maximum level as the circadian alerting signal (process C) diminishes. With ongoing sleep, the homeostatic drive dissipates, and wakefulness ensues as the circadian signal intensifies in the morning. Reprinted with permission from Elsevier, Inc (*see* Color Plate 10, following p. 650).

3. Insomnia

3.1. Definition

Insomnia has traditionally been regarded as a symptom of difficulty with sleep onset or maintenance. The DSM-IV-TR includes primary insomnia as an Axis I disorder, characterized by difficulty initiating or maintaining sleep, or nonrestorative sleep lasting at least 1 month. It must be associated with clinically significant distress or impairment in social, occupational, or other types of functioning and not be associated exclusively with another sleep disorder. It cannot be associated exclusively with a psychiatric disorder or be the direct effect of a substance or a general medical condition (1).

The ICSD-2 defines general criteria for insomnia as 1) a complaint of difficulty initiating sleep, difficulty maintaining sleep, waking up too early, or sleep that is chronically nonrestorative or poor in quality; 2) this occurs when there is otherwise adequate opportunity and circumstances for sleep; and 3) there is some form of daytime impairment attributable to the nocturnal complaint, such as fatigue, malaise, impairment of attention, concentration, or memory; social or vocational dysfunction or poor school performance;

mood disturbance or irritability; daytime sleepiness; motivation, energy, or initiative reduction; proneness for errors or accidents at work or while driving; tension, headaches, or gastrointestinal symptoms in response to sleep loss; and/or concerns or worries about sleep. Categories of insomnia include adjustment (acute) insomnia related to a particular stressor, paradoxical insomnia with no objective findings or daytime sequelae to support the nocturnal complaint, insomnia caused by mental or medical disorders, inadequate sleep hygiene, and insomnia caused by drug or substance use (15).

Closest to the primary insomnia of DSM-IV-TR are psychophysiological insomnia and idiopathic insomnia. The latter is distinguished by: 1) onset during infancy or childhood, 2) no identifiable precipitant or cause, and 3) persistence with no periods of sustained remission. The former must be present for at least 1 month, and include a conditioned, persistent sleep difficulty and/or increased arousal in the bed. There must be at least one of 1) excessive focus on and elevated anxiety about sleep, 2) difficulty falling asleep at the desired time in the bed or for planned naps, but with no such difficulty during other monotonous activities when sleep is not planned, 3) better sleep in novel situations away from home, 4) mental arousal in bed with intrusive thoughts or the perception of inability to stop thinking that prevents sleep, and/or 5) increased muscular tension in the bed with the perception of inability to relax sufficiently to permit sleep. In all cases, the sleep disturbance is not better explained by another sleep, medical, psychiatric, neurological, or substance use disorder (15).

3.2. Epidemiology

The median prevalence of insomnia seems to be 35% in the general population with 10 to 15% prevalence of moderate or greater severity, suggesting a possible diagnosis of primary insomnia. Insomnia symptoms tend to be more frequent in women and increase with age for all people (16). If daytime consequences are included with insomnia symptoms, the prevalence ranges between 9 and 15%. Dissatisfaction with sleep quality or quantity is reported by 8 to 18% of people and actual insomnia diagnoses probably occur in approximately 6% of the population, remaining stable across age groups, in contrast to the increase of insomnia symptoms (17). Despite the prevalence of insomnia, the majority of sufferers do not seem to discuss it with their primary care physicians (18–20). In the elderly population, serious insomnia may affect at least 20 to 40% of people (21–24).

3.3. Clinical Picture

Patients with primary insomnia typically present an insomnia complaint coupled with corresponding daytime symptoms. They commonly describe increased arousal at bedtime. This may relate to pain, urinary frequency, respiratory symptoms, heartburn, limb restlessness, ambient stimuli in the bedroom, sleep–wake schedule, medication history, and use of caffeine, alcohol, and/or tobacco. Reports from bed partners add considerable descriptive history. A sleep–wake diary is very helpful to characterize the ongoing pattern and variability of insomnia. Patients typically find the bed and bedroom increasingly associated with wakefulness and make efforts to "try to sleep." This cognitive arousal leads to autonomic arousal and both will interfere with sleep onset. Dysfunctional beliefs regarding insomnia, such as negative health risks, fear of death, loss of vitality, and/or loss of control over sleep causes many individuals to dread their nightly bed time and come to fear the ordeal of lying in bed without sleep (25). They endorse symptoms such as fatigue, poor motivation and concentration, mood disturbance, impaired psychomotor performance, and physical symptoms including headache, musculoskeletal difficulty, and gastrointestinal disturbance. Despite these symptoms, patients do not fall asleep during the day, reflecting a generally hyperaroused state (26–28).

In the elderly population, the most frequent interferences with sleep are pain, cardiovascular disorders, pulmonary diseases, urinary problems, dementia or other neurological disorders, psychiatric disorders, and the effects of medications, drugs, and alcohol (16, 23, 29–35).

3.4. Case History

A 46-year-old married man complains of persistent difficulty falling asleep. He retires gradually earlier, currently at 9:00 PM, in an effort to get enough sleep to allow him to work effectively as an executive in a local industry. He fears that insomnia will permanently impair his productivity and potential for advancement. In bed, he becomes increasingly preoccupied with recollections from the previous day and projected activities for the coming week. He puts great effort into trying to disregard these thoughts and will toss and turn for up to 2.5 hours before falling asleep. This pattern tends to recur after he awakens at 3 AM to urinate and then returns to bed. He awakens unrefreshed before his alarm sounds at 6:30 AM. He reports fatigue but does not fall asleep, even if attempting to nap during daytime hours. He feels sluggish, endorses poor concentration at his work, and his mood has become depressed and irritable. Although 10 mg zolpidem has been very helpful during past bouts of insomnia, he prefers now to avoid medication to maintain his participation in civil aviation. He agrees to eliminate caffeine consumption, write in a daily journal before bedtime, and restrict his sleep to between the hours of 12 midnight and 6 AM. Sleep onset and maintenance as well as daytime functioning begin improving during the next 4 weeks.

3.5. Laboratory Findings

Polysomnographic studies are rarely indicated for the evaluation of insomnia, and are reserved for cases unresponsive to therapy or if obstructive sleep apnea (OSA), parasomnias, or movement disorders are suspected (36). Quantitative electroencephalography has shown increased beta (fast frequency) activity and decreased theta and delta (slower frequencies) during sleep, suggesting increased cortical arousal (37, 38). Patients with insomnia have also been found to have increased physiological arousal, manifested by increased metabolic rate. Patients with paradoxical insomnia, previously called sleep state misperception, have lower metabolic rate than insomniac patients, but still more than healthy sleepers (39). The sleep–wake diary can be supplemented by actigraphy, recorded by a wrist-worn movement monitor that can be worn for days or weeks to indicate periods of rest and activity. This is particularly helpful to distinguish paradoxical insomnia with clear periods of apparent sleep, and circadian rhythm sleep disorders when there is aberrant timing of sleep periods (Fig.37.4) (40). Positron emission tomography (PET) performed with insomnia patients has shown greater global cerebral glucose metabolism during wakefulness and sleep, less decline with transition from wake to sleep in regions that promote wakefulness, and less relative metabolism in the prefrontal cortex while awake relative to healthy control subjects (41).

3.6. Clinical Course

Short-term insomnia is often related to psychosocial stress, medical disorders and their treatment, or circadian rhythm sleep disorders. It is usually time-linked with the apparent precipitating events, and treatment is focused on those causes. Some individuals are constitutionally predisposed to more fragile sleep capability. Most primary insomnia tends to be chronic, with longer than a 1-month duration (42–44). This disorder is related to similar predisposing and precipitating factors, but also perpetuating factors as patients come to anticipate and fear their inability to fall asleep or maintain sleep. Such perpetuating factors include violations of sleep hygiene by lying in bed trying unsuccessfully to sleep, using alcohol for sedation, using caffeine to enhance daytime functioning, and sleeping beyond a usual wake-up time in efforts to accumulate more sleep (45). Hence, there is a conditioned pattern

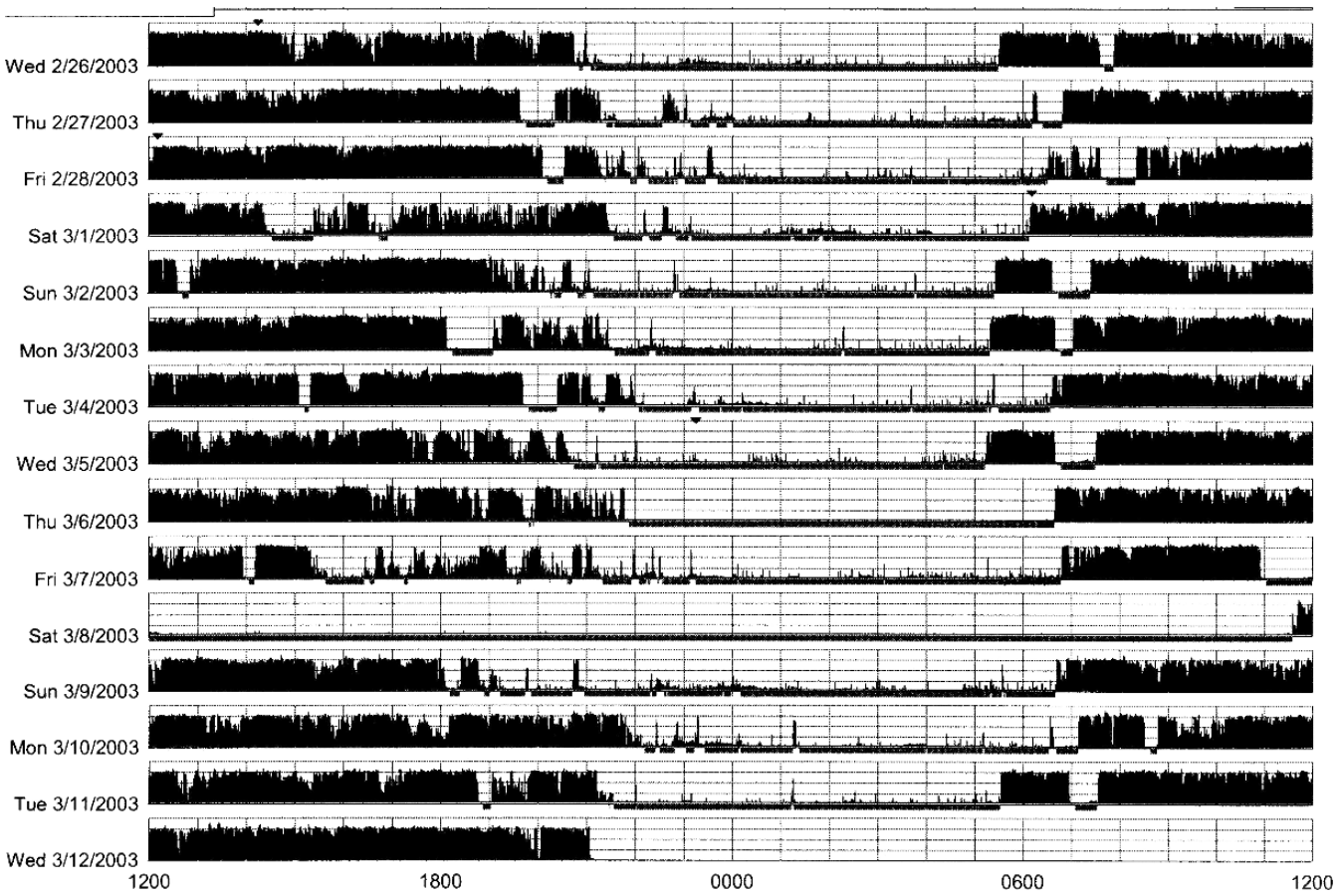

FIGURE 37.4. A wrist-worn activity monitor records movements in 1-minute time bins to display a representation of rest–activity (sleep–wake) cycling during a 2-week period. Note that during the period with absolutely no detectable movement, the device was not being worn. When coupled with a subjective sleep–wake diary, actigraphy can provide information from many successive days and nights.

of hyperarousal that develops in the situation in which sleep is sought and desired. Some individuals report disturbed sleep onset and maintenance since early childhood, which constitutes idiopathic (childhood-onset) insomnia (46).

3.7. Differential Diagnosis

As described above, most insomnia is temporally related to precipitating factors. When it does not seem to be independent of another condition, it can be described as comorbid, which does not necessarily imply causality or association. Insomnia must be distinguished from voluntary insufficient sleep syndrome and must occur despite adequate opportunities for sleep. Many drugs have been implicated to cause acute insomnia, including methylxanthines, stimulants, steroids, some antihypertensives, and some antidepressants such as bupropion and SSRI drugs. Their role in chronic insomnia has not been systematically studied (42).

Circadian rhythm sleep disorders involve shifts in timing of sleep propensity but the sleep that occurs during these periods is unremarkable. The delayed sleep phase type often presents with a complaint of insomnia, although the individual can easily fall asleep if not retiring to bed until the late hour, when sleepiness becomes apparent. In that case, the person is not likely to awaken until after a normal sleep duration. This can lead to inability to conform to a desired work or social schedule (47).

3.8. Etiology

The etiology of primary insomnia is not clearly understood. A familial contribution is suggested by 35% of patients having a family history of some sleep disturbance, most frequently insomnia. This is more likely when onset for the index case is before age 40 years and the predominant complaint is sleep onset difficulty (48). Abnormal elevations of urinary free cortisol levels reflecting elevated arousal are consistent with a sleep disturbance related to abnormal catecholamine metabolism (49). Not only is insomnia a ubiquitous symptom of depression, but also it seems from a few longitudinal studies that it is predictive of future incidence of depression (50–52). Exceptionally rare is a hereditary prion disease, fatal familial insomnia, resulting in neuronal loss and astrogliosis of the anterior medial thalamus and other structures. This produces severely disrupted sleep as well as dream enactment and other motor activation during sleep (53, 54).

Up to 40% of adults with insomnia in the general population (50) and approximately 75% of patients with insomnia in sleep center or primary care clinics have a psychiatric disorder (55). Approximately 71% of these will have dementia, 69% depressive disorders, 61% anxiety disorders, and 32% alcohol dependence (56). Polysomnographic studies of depression have shown diminished slow-wave sleep (stages 3 and 4), frequent nocturnal arousals and awakenings, as well as reduced time between sleep onset and the first REM period (57, 58). By PET imaging, there seems to be less cortical and thalamic deactivation in depressed patients compared with healthy control subjects as they undergo the transition from wake to sleep. This suggests a degree of cerebral metabolic activation that may be associated with the nonrestorative sleep complaint of patients with depression (59).

3.9. Treatment

Treatment of comorbid or secondary insomnia is directed at the underlying disorder. The sleep symptom may influence the choice of such therapy, such as a sleep-supporting antidepressant, analgesic, neuroleptic, antacid, etc. If insomnia persists despite initial therapy, an adjunctive hypnotic drug may be indicated. If insomnia persists with resolution of apparent secondary or comorbid disorders, then treatment as for primary insomnia should be initiated. Two basic treatment approaches are commonly used, cognitive–behavioral therapies and pharmacotherapy.

3.9.1. Nonpharmacological Therapy

Cognitive–behavior therapies (CBT) include techniques that have been demonstrated to counter the perpetuating factors responsible for continuing chronic insomnia. Various techniques are combined into an individualized program, which can be administered by psychologists, psychiatrists, nurses, and primary care physicians during an average of 3 to 10 sessions. A traditional element is stimulus control therapy, which acknowledges the bedroom as a conditioned stimulus for wakefulness where insomniac patients can remain for extended periods trying to sleep. Leaving the bedroom if not sleeping decreases the impact of this learned association. The bed is reserved for sleep or sexual activity and nothing else (60, 61). Another component, sleep restriction therapy, calls for reducing the time spent in bed to diminish wakefulness during that period and increase the homeostatic sleep drive, which derives from partial sleep deprivation (62). Relaxation training can be added to decrease arousal (63). These strategies are combined with a cognitive, psychoeducational approach to challenge feared consequences of sleep loss, revise expectations for normal sleep, and reinforce principles of sleep hygiene, such as regular sleep scheduling and modulation of caffeine use (64, 65). CBT is clearly effective for reduction of sleep onset latency and subsequent awakenings in at least 50% of patients (63, 66–68). Benefits seem to be sustained in studies of up to a year in duration and may be more enduring yet when hypnotic medication has not been prescribed (63, 69–71). Longer duration outcome studies are needed for all insomnia remedies, and it is remarkable that currently available evidence covers such short intervals in the case of a typically longstanding, chronic condition.

3.9.2. Pharmacological Therapy

3.9.2.1. Hypnotic Drugs

Pharmacotherapy has been used for insomnia since alcohol, chloral hydrate, and barbiturates have been known. Currently, the principal hypnotic agents are the benzodiazepines (BZ), BZ receptor agonists (BZRA), and the new melatonin agonist, ramelteon. The former two groups act at the BZ receptor site on the GABA-A receptor complex, closing the chloride channel and diminishing neurotransmission. The BZs currently approved in the United States for treatment of insomnia include flurazepam, triazolam, quazepam, estazolam, and temazepam. BZRAs include zolpidem, zaleplon, and eszopiclone. These drugs are all rapidly absorbed and variably metabolized and excreted. Two BZs, flurazepam and quazepam, have long durations of action with elimination half lives ($t_{1/2}$) of 48 to 120 hours. The BZRAs include an ultrashort duration drug, zaleplon, with a $t_{1/2}$ of 1.0 hour. All of the others are of intermediate (temazepam, estazolam, eszopiclone with a $t_{1/2}$ of 5–15 hours), and short duration (triazolam and zolpidem with a $t_{1/2}$ of 1.5–5 hours). As a rule, the longer-duration BZs can cause hangover sedation and should be reserved for patients requiring anxiolytic effect by day. These and the intermediate-duration drugs may be more useful for patients with sleep maintenance insomnia over the course of the night. Zaleplon, typically cleared within 4 hours, may be taken during the night if wakeful activity is not anticipated during that interval.

In healthy sleepers, BZs tend to decrease sleep onset latency, wake after sleep onset, stage 1 sleep, stage 3/4 sleep, and REM. They tend to increase total sleep time, sleep efficiency, stage 2 sleep, EEG fast activity, and latency to the first REM period. When studied exclusively in insomniac patients, predominant effects are increased total sleep time and reduced stage 3/4 sleep. Zolpidem has very little effect on the structure of PSG measured sleep other than shortening latency and increasing continuity (72). In a PSG study of insomnia treated with zolpidem, drug treatment lowered sleep latencies to persistent sleep from 61.9 ± 6.7 minutes to 23.7 ± 2.3 minutes (73).

Most studies of these agents have been conducted during short periods, typically up to 8 weeks, with the exception of intermittent dosing of zolpidem during 12 weeks, and nightly eszopiclone during a 6-month extension. These studies all document continuing efficacy without development of tolerance. Because most primary insomnia is chronic, physicians are apt to treat it with long-term use of hypnotic drugs, although there are no studies yet providing citable evidence (43, 74–76).

Many side effects are related to elimination half-life. Withdrawal effects including rebound insomnia (i.e., worse than pretreatment) are typically not seen with long-duration drugs and increase with decreasing half-life BZs (77–79). This is a transitory one- to three-night phenomenon when it occurs. It is not appreciably associated with BZRAs. Anterograde amnesia can be problematic and typically associated with the shorter-duration BZs and BZRAs. It is likely dose-related and has been particularly noted with triazolam (80, 81). Zolpidem has been associated with unusual sleepwalking with sleep-related eating (82, 83), as have risperidone and olanzapine (84, 85). It is possible that the perception of continuous, refreshing sleep is, in part, related to the anterograde memory inhibition of BZRAs (86).

Ramelteon is a melatonin-1 and -2 receptor agonist that is available in 8 mg dosage form. It has $t_{1/2}$ of 2 to 5 hours and no evidence of rebound insomnia, tolerance, or amnesia. It has been reported to benefit primary insomnia in younger and older adults (87, 88). Animal data has documented efficacy for re-entrainment of circadian rhythm sleep disorders (89).

3.9.2.2. Other Drugs

Many other drugs have been prescribed to treat insomnia. A large study based on a nationally representative Physician Drug and Diagnosis Audit of approximately 3,400 physicians during 2002 cites "drug occurrences" in millions for trazodone (2.7 million) as the most frequently prescribed agent for use as "hypnotic," to "promote sleep," or to "sedate night." This frequency of prescriptions is 32% more than for zolpidem (2.1 million), the second ranking drug, followed by amitriptyline (0.8 million), mirtazapine (0.7 million), quetiapine (0.5 million), olanzapine (0.2 million), hydroxyzine (0.3 million), doxepin (0.2 million), cyclobenzaprine (0.2 million), and diphenhydramine (0.2 million). Only 4 of the top 16 drugs were US Food and Drug Administration (FDA) approved for insomnia, not including clonazepam (0.4 million), alprazolam (0.3 million), and lorazepam (0.3 million), which are not so-approved, but which also appeared. Despite the low level of evidence for hypnotic efficacy of antidepressants, the author suggests that their favored status relates to product label limitations on duration of use of hypnotic drugs, their DEA schedule IV status, and their perceived liability for abuse and dependence. There is no substantial support in the literature to document such high risk (90, 91).

Trazodone, a weak selective serotonin reuptake inhibitor (SSRI), also inhibits 5-HT-1A, -1C, and -2 receptors. It is a moderate inhibitor of histamine-H1 receptors, but is not anticholinergic (92). Although trazodone may increase stages 3/4 sleep, it has little effect on REM. Although it may diminish sleep onset latency, increase total sleep time, and increase sleep efficiency in some studies of healthy control subjects or depressed patients, these effects were limited to a single week for insomnia patients (93–97).

SSRI agents are among the most widely prescribed antidepressants. They have long been known to suppress REM sleep. They also increase sleep fragmentation, with awakenings and stage shifts (98–100). A striking finding in patients treated with SSRIs is persistence of slow eye movements well into consolidated non-REM sleep. This is of unknown clinical significance, although it indicates an enduring neurophysiological response from previous exposure to SSRI drug. This can continue even long after the drug has been discontinued (101).

The tertiary amine tricyclic antidepressants (TCAs), doxepin and amitriptyline, inhibit histamine, acetylcholine, and alpha-1, and alpha-2 adrenergic receptors. Antihistaminic activity mediates sedation, whereas anticholinergic activity contributes to the inhibition of REM sleep seen with these drugs (102). Trimipramine does not seem to affect REM sleep. TCAs do have documented capacity to reduce sleep latency and improve sleep efficiency in healthy control subjects and depressive patients, but only limited data show improved sleep efficiency for primary insomnia (103–107).

In a large study of major depressive patients treated with nefazodone, a potent 5HT-2 inhibitor, there was a small but statistically significant increase in sleep efficiency and decreases in number of awakenings and wake time during sleep. Most notable is the absence of REM inhibition (100).

Mirtazapine is a potent antihistamine that also antagonizes 5HT-2, and alpha-1 and alpha-2 noradrenergic receptors. It seems to decrease sleep latency and increase stage 3/4 sleep in healthy adults, although not as clearly in depressed patients. Its sleep-favoring effects seem to be more potent at low doses, where antihistaminic effects may predominate (108–110).

Other antihistamines, such as diphenhydramine, that can act centrally to mediate sedation do not seem to be potent inducers of polysomnographic sleep. There also seems to be rapid tolerance to this effect. Coupled with anticholinergic, cognitive, psychomotor, and anorectic side effects, diphenhydramine is a less ideal hypnotic, despite its 16th place frequency of use in 2002 (90, 97, 111–114).

Ever since the days of sedating phenothiazines, sedating neuroleptic drugs have been used to enhance sleep. This is particularly useful during treatment of schizophrenic and affective psychoses, when control of insomnia is an integral component of acute therapy. More recently, atypical neuroleptics have been used in the same manner. No studies, however, address the use of these drugs for insomnia.

Clozapine is a 5HT-2A, -2C, -6, and -7 receptor antagonist as well as a 5HT-1A partial agonist, which may relate to its tendency to increase non-REM sleep. In a study of 36 schizophrenic patients, clozapine was associated with total sleep time of 432 ± 50 minutes in 12 patients, compared with 409 ± 40 minutes in the 10-patient classical neuroleptic group, and 361 ± 59 minutes in 14 drug-naïve patients. Sleep latency was 26 ± 34 minutes in the clozapine group, 13 ± 17 minutes in the classical neuroleptic group, and 56 ± 55 minutes in drug-naïve patients (115). Also in schizophrenic subjects, clozapine was associated with improved sleep continuity and increased stage 2 sleep, but no significant change of sleep latency from the beginning of therapy through at least 7 weeks of treatment (116). In another study of bipolar and schizoaffective disorders, clozapine was found to be associated with a lengthening of sleep latency, but data from this study also indicates that it is primarily a non-REM sleep enhancer with increased total sleep time and subjective reports of restedness (117).

Quetiapine is also a strong 5HT-2 antagonist as well as antihistaminic, antidopaminergic, and antiadrenergic agent. In a double-blind, placebo-controlled study of quetiapine in healthy subjects, doses of 25 and 100 mg were associated with significantly shortened sleep latencies, from 15.4 ± 12.5 minutes on placebo to 8.2 ± 5.2 minutes on 25 mg and 7.4 ± 5.7 minutes on 100 mg. Total sleep time increased from 433 ± 16 minutes (placebo) to 450 ± 7.4 (25 mg) and 446 ± 26 minutes (100 mg). Similar benefits were noted during a night of acoustic stress. There was an increase of periodic leg movements and decreased stage REM percent with the 100-mg dose (118).

Olanzapine, another potent 5HT-2A and -2C antagonist, also has affinity for muscarinic cholinergic, alpha-1 adreno-, and histamine H1 receptors. It is thought that the 5HT-2C receptor is involved in the regulation of non-REM slow-wave sleep, which was increased substantially in a study of healthy male adults and SSRI-resistant depressed patients (119, 120).

Risperidone, also a 5HT-2 blocker, has been shown to decrease REM sleep duration in healthy control subjects and treatment-resistant depressed patients in whom total and stage 2 sleep increased. It did not affect REM latency (121).

4. Movement Disorder: Restless Legs Syndrome

4.1. Definition

Although categorized as a sensorimotor or movement disorder, restless legs syndrome (RLS) is a frequent cause of difficulty falling asleep. Originally described by Ekbom (122), it remains an interesting and challenging clinical problem. Diagnostic features have been elucidated by an international RLS study group and the ICSD-2 diagnostic criteria for adults include: 1) urges to move the legs, usually because of or associated with discomforting sensations in the legs; 2) the urges or sensations begin or worsen with rest or inactivity; 3) they are partially or completely relieved during movement of the limbs; 4) they are predominantly or exclusively present during the evening or night hours; and 5) the symptoms are not related to any other sleep, medical, neurological, psychiatric disorder, or to medication or substance use disorders (15).

4.2. Epidemiology

RLS seems to be increasingly common, with a prevalence estimated to be 10 to 15% of the general population, and is more frequently found in women than men (123–127). It is found in 20% of pregnant women (128, 129), 20 to 62% of patients with chronic renal failure treated with dialysis (130, 131), and 5.2% of patients with polyneuropathy (132).

4.3. Clinical Picture

The core feature of this disorder is the strong or irresistible urge to move the legs, most typically in response to sensations

that are not easily described and/or painful, such as "creepy-crawly," "like bugs marching in my legs," or "like bubbles in the veins." These may occasionally extend into the trunk and upper extremities, and can be extremely uncomfortable. They are always worse in the evening and night, although they may emerge during relaxed wakefulness by day. Some patients will experience involuntary jerking of limbs, and most will have continuing repetitive, periodic movements of their limbs during sleep. At times, individuals will need to arise and walk about. Hence, this disorder can impact negatively on sleep onset as well as maintenance. Symptoms can vary in frequency from nightly to intermittent (133, 134).

4.4. Case History

A 33-year-old woman complains of difficulty falling asleep for many years. This worsened during each of her two pregnancies and improved for a period of time when iron supplementation was prescribed during the month preceding her last delivery and the subsequent 3 months. She was said to have suffered "growing pains" during adolescence and remembers similar but milder leg discomfort at night during her youth. She retires to bed around 10 PM, and, with relaxation, her legs feel increasingly "antsy" and she cannot find a comfortable position without stretching and moving them, occasionally placing a pillow between her knees. Frequently, she will get up and walk in circles around her living room before returning to bed. She falls asleep after 60 to 90 minutes and her husband says that her legs continue to move at intervals while she is asleep. He must leave the bed and sleep elsewhere approximately twice weekly because of this. She reports similar discomfort during attempted late afternoon naps, but with less intense need to move. She has requested help because of increasing daytime fatigue, irritability, and worry about her ability to care for her children. Neurological examination is unremarkable. Mood is mildly depressed but without any history or family history of depressive disorder. Her hemoglobin level is 14.1 mg/dl and serum ferritin is 87 μg/L. After beginning 0.125 mg pramipexole taken 2 hours before bedtime and increasing to 0.375 mg, she reports improvement of sleep onset and daytime symptoms.

4.5. Laboratory Findings

There are often no clinical laboratory findings unless peripheral iron deficiency is present. Serum ferritin, a measure of iron storage, can be reduced in cases of blood loss, such as menorrhagia, gastrointestinal bleeding, and frequent blood donations. Concentrations below 45 μg/L can be associated with increasing severity of RLS (134–138). Polysomnographic studies of sleep in patients with RLS demonstrate periodic leg movements during sleep (variably associated with EEG arousals) and initial wakefulness in 80 to 90% of cases (139). Another diagnostic procedure is the Suggested Immobilization Test (SIT), which monitors leg movements polygraphically with the patient seated upright on a bed at usual bedtime. A total of more than 40 periodic leg movements during wakefulness supports the diagnosis of RLS (140). Actigraphic monitoring of periodic leg movements has also been used (141).

4.6. Clinical Course

RLS may occur at all ages and can be misdiagnosed as "growing pains" in children (142, 143). When beginning before age 45 years, symptoms progress slowly from an intermittent to a more frequent pattern and may become daily by 40 to 65 years of age. Late onset RLS progresses much more rapidly. Symptoms typically begin in the feet and legs but may progress, in some patients, to the trunk and upper extremities. They have a marked circadian pattern of evening and nocturnal worsening. They may occur by day, especially when the patient is inactive, such as during long periods of enforced seating in a vehicle, theater, or work setting (123, 144).

4.7. Differential Diagnosis

Traditional neuroleptic medications antagonizing dopamine receptors may induce akathisia resembling RLS, but with more generalized body restlessness and absence of prominent circadian variation. The neurological condition of painful legs and moving toes is also not diurnally variable, nor is it associated with an urge to move. Discomfort related to positional effects of the body on a supporting surface includes no urge to move and is resolved by change of position. Sleep starts, or hypnic myoclonia, are normal involuntary movements limited to the moment of transition between wake and sleep and with no urge to move. They can be associated with bursts of visual and auditory sensations in some individuals. Sleep-related leg cramps involve actual muscle spasm and require stretching and recovery time rather than simple movement for improvement. Although some RLS is experienced as painful, movement as a response to pain from various sources is not typically based on an urge to move per se (15). Insomnia with anxiety and psychomotor agitation is likewise not associated with an urge to move or relieved by it.

4.8. Etiology

There is a genetic predisposition with a familial distribution of RLS, which occurs three to six times more frequently in first-degree relatives of affected subjects than in the general population. An autosomal dominant transmission has been described in some families. There tends to be more genetic contribution with younger age of onset (15, 139). The pathological basis of RLS is likely related to deficient brain iron acquisition by the neuromelanin cells in the substantia nigra.

Decreased iron availability in these cells may compromise dopaminergic function by limiting synthetic enzyme activity or the expression of dopamine transporters or receptors (145). A genetic variant on chromosome 6p21.2 has been found to be associated with susceptibility to RLS with periodic limb movements during sleep and inversely associated with iron stores (379). As noted above, RLS occurs frequently in patients with iron deficiency, severe renal disease, and pregnancy. Peripheral neuropathy is often associated with RLS, and its associated pain may contribute to the urge to move. When measured, cerebrospinal fluid (CSF) ferritin levels have been 65% lower than normal peripheral levels in patients with RLS, suggesting specific brain iron deficiency (146). A decreased density of dopamine D-2 receptors has been observed in the striatum of RLS patients by PET and single-photon emission computed tomography (SPECT) imaging (147–149). Many sedating antihistamines, numerous antidepressant drugs (other than bupropion with its dopaminergic property), and dopamine antagonists will precipitate or worsen RLS (15, 150).

4.9. Treatment

A treatment algorithm has been proposed, based on the frequency of RLS symptoms (134). For mild, intermittent RLS, nonpharmacological strategies are useful. If appropriate, mentally alerting activities may reduce daytime symptoms. Trial restrictions of caffeine, nicotine, and alcohol may be instituted, and selected drugs, such as antidepressants, may be eliminated if safely possible. Replacement of iron should be prescribed if serum ferritin levels are less than 20 μg/ml and considered if ferritin is less than 50, which has been associated with worsening of RLS (135, 137). The initial pharmacological strategy for intermittent symptoms is typically prescription of a dopaminergic agent. The initial choice could be 25 mg carbidopa plus 100 mg levodopa, as needed, but alternatives include dopamine agonists, 0.125 mg pramipexole or 0.5 mg ropinirole, taken 2 hours before bedtime, as needed, and titrated further as indicated (151–154). Open-label polysomnographic studies of pramipexole and a large double-blind, placebo-controlled study of ropinirole document effectiveness of these dopamine agonists for treatment of subjective (insomnia) and objective (limb movements) features of RLS. Other options include the low-potency opioids, propoxyphene or codeine; the opioid agonist, tramadol; the BZs, temazepam or triazolam; or the BZRAs, zolpidem or zaleplon, which may be considered as needed.

For RLS occurring nightly, regularly administered therapy is needed and includes the same nonpharmacological techniques as well as a nightly dopamine agonist, gabapentin, or low-potency opioids. Refractory RLS may develop with inadequate or decreasing benefit from dopamine agonists, intolerable side effects, and/or augmentation of RLS symptoms, causing occurrence earlier in the day. For these challenging cases, change to gabapentin or a different dopamine agonist is considered, or a second agent from the list above can be added. An important side effect of dopamine agonist therapy is the emergence of impulse control disorders, such as compulsive gambling, buying, and sexual behavior, which has been reported in patients with Parkinson's disease on these drugs. All patients treated with dopamine agonists must be warned about this risk, which can occur in as many as 4 to 8% of patients (155–157). Change to a high-potency opioid or tramadol may be needed (134). In severe cases of RLS, both associated with prominent leg pain or not, methadone therapy on a long-term basis may be required as a monotherapy or combined with a dopaminergic agent (158).

5. Obstructive Sleep Apnea

5.1. Definition

Among the breathing-related sleep disorders in the DSM-IV-TR are the respiratory drive disturbances known as central sleep apnea syndromes related to neurological and cardiovascular disorders, respiratory depressant drugs (e.g., opioids), and high altitude environments. Sleep may also be disturbed by non-obstructive alveolar hypoventilation in cases of pulmonary disease, such as lower airway obstruction, as well as neuromuscular and chest wall dysfunction. The most common breathing-related sleep disorder is obstructive sleep apnea (OSA). Although not formally defined in the DSM-IV-TR, it is designated as a condition resulting in excessive sleepiness or insomnia, and not accounted for by another mental disorder, substance, or medical condition (1).

The ICSD-2 defines OSA as marked by at least 1) complaints of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, or insomnia, OR 2) wakenings from sleep with breath holding, gasping, or choking, OR 3) bed partner reports of loud snoring, breathing interruptions, or both during the patient's sleep, AND polysomnographic evidence of five or more scoreable respiratory events per hour of sleep. These respiratory events are apneas or hypopneas (10 second periods of complete or partial cessation of air flow) if there is evidence of respiratory effort during all or a portion of each event, or respiratory effort-related arousals (RERAs), if EEG arousals are associated with crescendo snoring or decreased oronasal air flow. In either case, the disorder may not be better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder. Alternatively, the diagnosis may be applied in the absence of symptoms if there is polysomnographic evidence of 15 or more of these scoreable events per hour of sleep (15).

5.2. Etiology

The basis of OSA is sleep-disordered breathing (SDB) caused by the collapse of the pharyngeal airway space when negative

intraluminal pressure caused by the diaphragm during inspiration overcomes the capacity of the throat dilator muscles tensing the palate and holding the tongue forward to hold the space open. Additional pressure on the airway from soft tissue and bony structures also adds force to constrict the airway. The more soft tissue relative to the size of the bony compartment (e.g., obesity), the more additional extraluminal pressure there is to collapse the airway. Craniofacial abnormalities such as small mandible, macroglossia, retrognathia, and acromegaly also predispose to OSA (159). Airway size is further reduced in the presence of obstructing tissue such as tonsils and adenoids. Body position during sleep can influence this by force of gravity. When sleep occurs, there is less dilator muscle response to negative pressure of inspiration. Further, lung volume diminishes during sleep and this decreases traction on the airway, creating further vulnerability (160). Obesity is common and a linear correlation has been established for neck girth and severity of OSA (161, 162).

If there is minimal airway collapse, snoring alone can occur with tissue vibration but no alteration of airflow. With more compromise of airway patency, there can be varying degrees of airflow limitation and increased inspiratory effort that can lead to RERAs. These may be inferred from a pattern of crescendo snoring on successive preceding breaths, characteristic flattening pattern on a nasal pressure monitor of airflow during sleep, or from increased intrathoracic pressure on esophageal manometry, which is not frequently used in conventional PSG. These events typically interrupt sleep continuity without significant drop in tidal volume or change in oxyhemoglobin saturation as measured by transcutaneous colorimetric oximetry. Further increasing of airway obstruction can compromise actual airflow and result in partial (hypopnea) or complete (apnea) interruption. These events result in lowering arterial partial pressure of oxygen (PaO_2), leading to desaturation of oxyhemoglobin.

Such sleep fragmentation and intermittent hypoxia after these events may also contribute to development of hypersomnia, the hallmark symptom of OSA. The apnea–hypopnea index (AHI), or hourly frequency of these events, is the most typical metric cited in published studies. The term respiratory disturbance index (RDI) is not often well defined and may refer to AHI or to the rate of all three types of obstructive respiratory events. AHI of 5 to 15 events/hour would generally be considered as mild, 15 to 30 events/hour, moderate, and at least 30 events/hour, severe OSA. When these events occur with clinical symptoms, the condition is designated as obstructive sleep apnea syndrome (OSAS).

5.3. Clinical Picture

The clinical presentation of OSAS includes reports of snoring, often with apneas witnessed by bed partners, and excessive daytime sleepiness (163). Sleepiness refers to the tendency to fall asleep in contrast to fatigue during intact wakefulness. It can be assessed by a questionnaire such as the Epworth Sleepiness Scale, although this has modest correlation with the AHI (159). Sleepiness symptoms can include falling asleep ("dozing") during activities such as sitting and reading, watching TV, sitting inactive in a public place, as a passenger in a car for 1 hour, lying down to rest in the afternoon, sitting while talking with someone, sitting quietly after lunch without alcohol, and in a car when stopped for a few minutes in traffic (164, 165). The degree of objectively measured sleepiness (presumably related to sleep fragmentation) varies with the AHI within individuals (166). The multiple sleep latency test (MSLT) has demonstrated evidence of this with mean latencies to sleep onset during four or five nap opportunities of 6.8 ± 4.2 minutes, clearly less than 11.6 ± 5.3 minutes after therapy (167). Still, however, only 35% of individuals with AHI of at least 30 events/hour may report symptomatic sleepiness (166). The most dramatic negative outcome of excessive sleepiness is drowsy driving (168–170). Although there is evidence that drivers with OSA have higher accident rates and less driving-based cognitive performance than control subjects, the statistical relationships with AHI are not strong (171–177). A validated questionnaire has shown usefulness for diagnosing OSAS based on presence and frequency of snoring, daytime sleepiness or fatigue, and history of obesity and hypertension. It predicts a high risk of OSA when symptoms are persistent and frequent in any two of these three domains (178).

Psychiatric disorders must also be considered in the clinical evaluation of OSA. Individuals with major depressive disorder have a fivefold higher likelihood of having DSM-IV-defined breathing-related sleep disorder than nondepressed persons, even when controlled for obesity and hypertension. Approximately 20% of individuals with one of these disorders seem to have the other as well (179). A longitudinal study has shown that, as OSA worsens from minimal to mild, the likelihood of developing depressive symptoms by the Zung depression scale increases by nearly 1.8-fold. When compared with healthy control subjects in that study, incidence of depression increased by factors of 2 for mild and 2.6 for moderate or worse sleep-related breathing disorder (180). In a cross-sectional study at a large Veteran's Administration medical center, patients with OSAS had statistically significantly increased prevalence of a number of psychiatric disorders when compared with patients without OSAS. Odds ratios were 2.67 for depressive disorders, 16.67 for anxiety disorders, 11.85 for PTSD, 5.13 for psychotic disorders, 4.06 for bipolar disorder, and 2.13 for dementia (181). The fatigue associated with comorbid depression may itself account for some of the symptomatology of OSAS when the two conditions overlap (182–184). This relationship is supported by the improvement of depressive symptoms with treatment of OSAS (185–187).

Neuropsychological disturbances have been reported in OSAS. Deficits of attention, concentration and vigilance, manual dexterity, visuomotor skills, memory, verbal fluency, and executive function have been documented and seem to

be mildly or moderately associated with severity measures by PSG. Daytime sleepiness as well as nocturnal, accumulated intermittent hypoxemia probably contributes to problems with memory, problem solving, and executive functioning (171, 188). Vigilance and attentional capacity deficits most resemble the effects of chronic partial sleep loss (189, 190). A large meta-analysis has shown untreated OSA to have no significant effect on intellectual and verbal functioning but significant effects on vigilance and executive functioning. Memory was less uniformly affected. Fine motor coordination and drawing are more vulnerable to the effects of OSA than tests of fine motor speed or visual perception (191).

5.4. Epidemiology

Widely cited information regarding epidemiology of OSA comes from a number of groups, including the Wisconsin Sleep Cohort and the multicenter longitudinal Sleep Heart Health Studies that have been underway for many years. These data, generally based on internally consistent definitions and methodologies, permit the conclusion that 20% of normal-weight white adults in the United States have AHI of at least 5 events/hour and 6.7% have AHI of at least 15 events/hour. Up to 5% of adults are likely to have OSAS with respiratory obstruction, daytime sleepiness, and/or other symptoms. Prevalence among women is approximately half of this, although their risk increases with postmenopausal status. Predisposing features include obesity, advancing age, and snoring (192–195).

5.5. Case History

A 48-year-old single man with chronic schizophrenia is noted to fall asleep during group sessions at his psychiatric day treatment program. His weight had increased over a decade to 280 pounds, for a body mass index of 39.75. He reports difficulty remaining awake whenever sedentary and has become drowsy when driving, although he denies any accidents. He is the sole driver in the home that he shares with elderly parents and a chronically ill sister. He reportedly snores, snorts, and gasps during the night, but there is no bed partner to describe any witnessed apneas. He is treated for severe hypertension, congestive heart failure (CHF), gastroesophageal reflux disorder, noninsulin-dependent diabetes, and schizophrenia. On PSG, he is found to have an AHI of 80 events/hour with an oxyhemoglobin desaturation nadir of 78%. Continuous positive airway pressure (CPAP) at 18 cm is effective, but he is unable to tolerate the mask despite extensive attempts at desensitization and numerous mask configurations. Titration with bilevel positive airway pressure is tried, but is likewise rejected by the patient. He then undergoes surgical revision of the soft palate with removal of the uvula (uvulopalatopharyngoplasty), again without improvement. Ultimately, he is treated with tracheostomy and experiences marked improvement in nocturnal sleep and daytime alertness.

5.6. Laboratory Findings

PSG in an attended laboratory situation is still the standard means of evaluating breathing during sleep. Typical obstructive events are recorded as in Fig. 37.5. Additional limited diagnostic instruments are being developed and have demonstrated usefulness for cases with high pretest probability in patients who are being evaluated for obstructive sleep apnea. These include cardiopulmonary monitors of respiration only, portable PSG, and peripheral arterial tonometry (PAT), which measures autonomic manifestations of respiratory obstructive events (196, 197, 380).

The overall total of apneas, hypopneas, and RERAs per hour describes the rate of sleep fragmentation relevant to subsequent daytime dysfunction (198). Formerly, the disruption of sleep caused exclusively by RERAs was known as upper airway resistance syndrome (UARS) and recognized as a cause of daytime sleepiness (199). It is now subsumed under the diagnosis of OSAS.

5.7. Clinical Course

OSA can begin in infancy and may be related to craniofacial anatomy and nasal airway deficiency (200). In children and adults, adenotonsillar hypertrophy can often account for the emergence of the disorder. Typically, OSA increases with age, although elderly individuals may have fewer daytime symptoms than middle-aged counterparts (201). During an 8-year follow-up study in the Wisconsin Sleep Cohort, the AHI increased in all groups, including healthy control subjects, but most prominently in those with obesity and habitual snoring subjects (195).

The association of OSA with increased mortality has been clearly documented since 1988, when patients with an apnea index greater than 20 were observed to show clearly elevated mortality compared with those having a lower apnea frequency. This was particularly true in patients younger than 50 years. None of the patients treated with tracheostomy or continuous positive airway pressure (CPAP) died during the decade when they were under study (202).

With ongoing exposure to OSA, patients have been found to have increasing cardiovascular risk with elevated heart rates, increasing blood pressure variability, and blunted heart rate variability (203). Hypertension is associated with OSA, in part relating to vasoconstriction responsive to elevated endothelin function and decreased levels of nitric oxide (204, 205). Oxidative stress and inflammatory processes may be proponents of the cardiovascular risk (159). There is a clear relationship between OSA and the development of hypertension

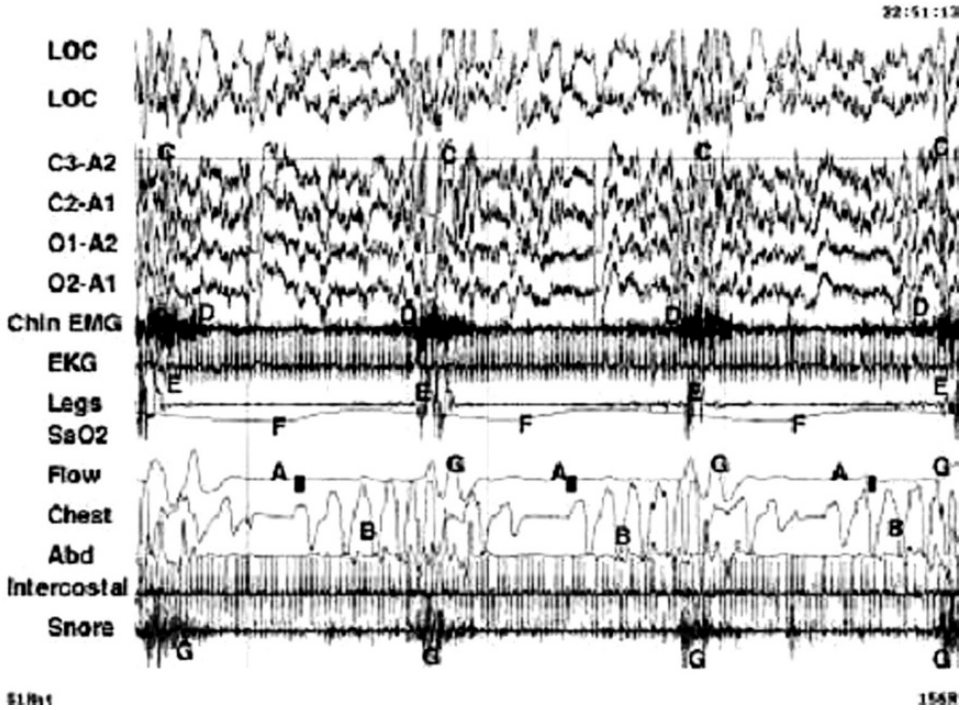

FIGURE 37.5. A 2-minute window demonstrates four obstructive apneas, with cessation of air flow (*A*) in the presence of persisting thoracic and abdominal manifestations of respiratory effort (*B*). These events are followed by EEG arousal (*C*) and bursts of chin muscle tone (*D*), leg movements (*E*), desaturations of oxyhemoglobin (*F*), and resumption of airflow with snoring (*G*).

(206). This may be the predominant influence on the development of congestive heart failure (CHF), which has long been recognized as a risk of chronic, untreated OSA. At least 10% of patients with CHF have OSA (207), and these patients may report lesser degrees of daytime sleepiness than those without CHF (208). Many patients with OSA have atrial fibrillation, but it is not yet clear whether this is of etiological relevance in either direction (209). Additionally, insulin resistance, diabetes, and increased leptin levels occur more in patients with OSA than in weight-adjusted comparison subjects (210, 211).

5.8. Differential Diagnosis

Other causes of excessive daytime sleepiness, such as narcolepsy, idiopathic hypersomnia, insufficient nocturnal sleep, and sleepiness related to medical and/or pharmacological factors must be considered. Other sleep-related breathing disorders are the central sleep apnea syndromes, such as appear in some neurological disorders, Cheyne–Stokes respiration of CHF, high altitude, and exposure to opioids. These all may certainly coexist with OSA in many cases.

5.9. Treatment

Before the introduction of CPAP, the primary therapy for severe OSA was tracheostomy. This produces immediate benefit caused by bypass of the upper (pharyngeal) airway space, allowing unimpeded ventilation. Weight loss for overweight patients remains a strong component of therapy, although success is difficult to achieve. Hence, bariatric surgery and other means of weight loss have been used with definite improvement (195, 212). The standard treatment for OSA is CPAP, developed in the 1970s to provide a pneumatic splint for the upper airway by administration of positive pressure through a nasal or oronasal mask interface (213). Pressure is initially determined by titration during PSG, although a number of automated CPAP machines are available to adjust pressure based on machine response to airflow obstruction. The advantage of PSG is the direct observation by technologists who can control mask leak, observe the effects of body position and sleep stage, and clearly distinguish periods of sleep from those of wakefulness. CPAP use distinctly improves daytime sleepiness (214, 215). Although long-term outcomes are not clearly known, CPAP in the short term has been shown to improve endothelin levels and blood pressure (205, 208, 216, 217), nitric oxide levels (218), glucose intolerance (219, 220), leptin levels and central obesity (221), left ventricular ejection fraction (208), urinary catecholamine levels (222), and the recurrence rate of atrial fibrillation (223). Unfortunately, adherence to nightly use of CPAP remains much less than desired for many reasons, including claustrophobia, interface failures, and other determinants of motivation (224). Some patients can use desensitization techniques but others may ultimately be unable to benefit from CPAP (225).

When clear anatomical obstruction, such as adenotonsillar hypertrophy or mass lesion is present, surgery is indicated. In patients unable to use CPAP, various surgical procedures have been used. Uvulopalatopharyngoplasty alone is frequently ineffective (226). When done in combination with establishment of forward tension on the base of the tongue, efficacy can be increased. In cases of severe maxillofacial abnormality, advancement of both maxilla and mandible can be performed (227–229). Oral appliances that hold the mandible in an advanced position during the night can be effective (198). Patients demonstrating OSA exclusively during sleep in the supine position may benefit by training to sleep only on either side. There is, as yet, no pharmacological therapy for OSA. Patients experiencing residual sleepiness after treatment of OSA have been shown to benefit from modafinil (230).

6. Hypersomnia

6.1. Definition

The DSM-IV-TR distinguishes two basic categories of disorders of excessive sleepiness, primary hypersomnia, and narcolepsy. The former is described as 1) excessive sleepiness for at least 1 month (or less if recurrent) with either prolonged sleep episodes or daytime sleep episodes almost daily, 2) causing clinically significant distress or impairment in social, occupational, or other areas of functioning. It is 3) not caused by insomnia, any other sleep disorder, insufficient amount of sleep, 4) any psychiatric disorder, or 5) any substance or general medical condition. The recurrent form includes periods of sleepiness lasting at least 3 days several times annually for at least 2 years. Narcolepsy is defined as 1) irresistible attacks of refreshing sleep occurring daily over at least 3 months with 2) one or both of cataplexy (spells of diminished muscle tone) and/or recurrent intrusions of presumed REM sleep components into the transition between sleep and wakefulness. These are hypnagogic (at sleep onset) or hypnopompic (at sleep offset) hallucinations or sleep paralysis at the beginning or end of sleep episodes. The disturbance is 3) not caused by a substance or general medical condition (1).

The ICSD-2 distinguishes hypersomnias of central origin from other disorders causing excessive daytime sleepiness such as circadian rhythm sleep disorders, sleep-related breathing disorders, or other causes of disturbed nocturnal sleep. In this nosology, primary hypersomnia of DSM-IV corresponds most directly with the category known for many years as idiopathic hypersomnia. The variant of this, which was previously designated as the polysymptomatic form, is now known as idiopathic hypersomnia with long sleep time. It is defined as 1) a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months. History, sleep logs, or actigraphy reveal 2) prolonged (longer than 10 hours) nocturnal sleep time and difficulty awakening fully from any diurnal or nocturnal sleep, and 3) no alternative causes are revealed by overnight PSG, which demonstrates 4) short sleep latency and longer than 10 hours of total sleep time. If MSLT is performed, 5) it reveals mean sleep latency less than 8 minutes and fewer than two sleep onset REM periods (SOREMPS) on four or five nap opportunities. In contrast, idiopathic hypersomnia without long sleep time is defined by 1) the same complaint of excessive daytime sleepiness, 2) habitual sleep of longer than 6 but shorter than 10 hours, 3) with exclusion of other sleep disorders by PSG, which 4) demonstrates a normal overnight sleep duration longer than 6 and shorter than 10 hours. MSLT must be performed and reveals 5) mean sleep latency less than 8 minutes and fewer than two SOREMPS (15).

Narcolepsy is divided into cases with and without cataplexy. In either case, there is a complaint 1) of excessive daytime sleepiness almost daily for at least 3 months. In the former case, there is 2) a definite history of cataplexy and 3) the diagnosis is, whenever possible, confirmed with nocturnal PSG and MSLT with mean sleep latency less than 8 minutes and SOREMPS recorded on at least two naps. Alternatively, a CSF hypocretin level at most 110 pg/ml or one third of mean healthy control values is diagnostic. In narcolepsy without cataplexy, there is 1) the same complaint of daytime sleepiness, but 2) cataplexy is absent, doubtful, or atypical. 3) PSG and the same MSLT findings are required. In both cases, 4) the sleepiness cannot be better explained by another sleep, medical, neurological, or psychiatric disorder, nor any substance or medication (15).

6.2. Epidemiology

Excessive daytime sleepiness as a nonspecific symptom may be reported by as many as 15% of the general population, but varies between studies and countries. Prevalence of combined varieties of specifically central nervous system-mediated sleepiness is more difficult to establish and may range from as high as 2 to 3% to less than 1% of the population (231). In a large-scale telephonic inventory, as many as 1.6% of a European and United Kingdom sample nap at least twice a day. Cataplexy seemed to be overestimated at 1.6% of the same population, because most subjects who reported it did not endorse sleepiness. Diagnosable narcolepsy seemed to have a prevalence of 0.047% (232). Two other studies of narcolepsy in Italy and Finland have described prevalence between 0.026 and 0.04% (232). In Israel, prevalence as low as 1:500,000 to 1:660,000 has been reported (233), whereas, in Japan, it has been as high as 0.16% (234). A retrospective study of narcolepsy in Olmstead County, Minnesota reports a prevalence of 0.056% (0.036% for narcolepsy with cataplexy, and 0.021% those without) (235). Prevalence of idiopathic hypersomnia seems to be approximately 10% of the rate for narcolepsy (236).

6.3. Clinical Picture

The central feature of disorders of excessive sleepiness is the tendency to fall asleep during the wake phase of an individual's day or to experience prolonged nocturnal sleep and/or daytime napping. This is distinct from a perception of fatigue but lacking the tendency to fall asleep even for a few minutes. Symptomatic sleepiness is based on self-report but corroborative history from family or friends is valuable. It usually corresponds with a score of 12 or greater on the Epworth Sleepiness Scale, but this is not definitive (164, 165). Idiopathic hypersomnia patients never develop cataplexy or nocturnal sleep disturbance (236). Naps, unlike for narcoleptics, are unrefreshing and may be prolonged (237). For some patients, not only is arousal from sleep difficult, but also it can be accompanied by irritability, confusion, and motor discoordination that has been called "sleep drunkenness" (238).

The classic primary hypersomnia condition, narcolepsy, was first described in France by Gélineau in 1880. He described two core symptoms of "narcolepsie" or sleep attacks and periods of "astasie" or sudden loss of muscle tone now known as cataplexy (239). Cataplexy is a relatively brief period of diminished or lost motor tone typically precipitated by emotion, most frequently laughter (240). It can cause loss of upright posture when seated or standing but may be as mild as drooping facial muscles or slurred speech. Weakness is bilateral and there are absent deep tendon reflexes during spells (241). These core symptoms become a tetrad in later literature, with subsequent addition of sleep paralysis, or waking from sleep with persisting loss of muscle tone, and hypnagogic or hypnopompic hallucinations (242). These so-called accessory symptoms represent components of normal REM sleep (muscle atonia and dream imagery), which become dissociated from the parent physiological state to appear abnormally during wakefulness (cataplexy) and transitions into or out of sleep (hypnopompic hallucinations, sleep paralysis).

More recently, spells of automatic behavior (unrecalled, often nonsensical or "absent minded") have been described (237). Also mentioned are disturbed continuity of nocturnal sleep, which is less problematic in young patients, and increases with advancing age. Unwanted periods of sleep tend to occur after a few hours of wakefulness and may last for minutes up to an hour. Nocturnal sleep and daytime naps are generally experienced as refreshing (243).

Narcoleptic symptoms can be misinterpreted as psychiatric, such as cataplectic gait disturbance diagnosed as psychogenic (244), and hypnopompic hallucinations as schizophrenic (245,246) or psychotic features of bipolar disorder (247,248).

6.4. Case History

A 30-year-old single man began falling asleep during classes in high school. He was regarded as a "weird kid" who would fall asleep even in the company of friends listening to music or watching sporting events. He graduated from college after 6 years of study but found it difficult to remain awake during classes. He began carrying large containers of coffee to lecture halls and the library. When he was 19 years old, he experienced the onset of unusual spells of weakness and slurred speech when caused to laugh by his friends. They knew that he could be made to appear drunk without having consumed any alcohol. He began socializing less because his friends would provoke him with jokes and gags to precipitate this. More and more, he struggled to remain sedate and aloof from others, for fear of "losing control" and being forced to sit slumped in a chair, unable to move either arm, or stand without support. His parents considered him to be "odd but sensitive" and tried to protect him. They encouraged his social withdrawal despite the fact that all who knew him regarded him as sensible and kind. He has intense interests in music, politics, and sports. During a visit to his physician for evaluation of earache, he falls asleep during the examination, and is then referred to a sleep disorders center. Overnight PSG is unremarkable other than REM latency of 45 minutes. On MSLT, mean sleep onset latency is 2.7 minutes, with clear REM sleep during three of four naps. After partial improvement of wake maintenance on 400 mg modafinil daily, his medication is changed to 40 mg methylphenidate daily with remarkable benefit. Cataplexy finally remits after the addition of imipramine, titrated to 25 mg twice daily.

6.5. Laboratory Findings

PSG findings that confirm the diagnosis of narcolepsy include adequate nocturnal sleep hours, possible early onset of the first REM period, and no identifiable cause of daytime sleepiness. MSLT is begun 2 hours after final morning awakening from the PSG study. With similar physiological monitoring, patients are observed during four or five 20-minute nap opportunities. The time between the beginning of each nap to onset of the first stage of scorable sleep is determined. If sleep occurs, it is observed for 15 minutes for scoring of sleep stages before awakening the patient. In the case of narcolepsy, hypersomnia is evidenced by mean sleep latency at most 8 minutes as well as the occurrence of REM sleep (SOREMPS) during at least two naps (167).

A variation of the MSLT protocol has been developed to monitor the capacity of individuals to remain awake, but is not used for diagnosis. The maintenance of wakefulness test (MWT) is conducted with the patient instructed to remain immobile while seated on a bed in a darkened, quiet room. The patient is told to remain awake during four sessions of 40-minutes duration. The onset of any sleep is scored as in the MSLT, but no sleep is allowed to accumulate. If no sleep is recorded, the test is consistent with the strongest objective indication of intact capacity to remain awake, whereas a mean sleep latency of less than 8 minutes indicates abnormal sleepiness. Scored for the first epoch of any sleep stage, mean

latencies between 8 and 40 minutes are of uncertain clinical significance (248).

The use of a wrist-worn activity monitor coupled with a subjective sleep–wake diary can help evaluate the possibility of chronically insufficient sleep (249). Changes of pupillary diameter and light response have been used to assess nonspecific sleepiness, which is associated with miosis (250, 251).

Narcoleptic patients with cataplexy have been found to have high (85–90%) presence of a human leukocyte antigen (HLA) allele, DQB1*0602, present in only approximately 25% of the general population. Approximately 40% of narcoleptic patients without cataplexy carry this allele (252, 253). More recently, determination of hypocretin (orexin) concentration in CSF has been helpful in distinguishing narcolepsy with cataplexy, for which an undetectable level is a highly specific finding. This specificity is limited to classic narcolepsy with cataplexy in the presence of the HLA DQB1*0602 allele. Detectable or normal CSF hypocretin levels are found in cases of narcolepsy without cataplexy and those with cataplexy but without the HLA marker (254, 255).

6.6. Clinical Course

Idiopathic hypersomnia probably presents before 30 years of age. Sleepiness is continuous during the day but with less intense "sleep attacks" than in narcoleptics (236). Spontaneous remission is unlikely. The onset of narcoleptic symptoms typically occurs around the time of puberty, with peak incidence rate in the second decade (235). Many fewer cases develop in the 4th and 5th decades. The correct diagnosis is frequently delayed by up to 10 years (256). Cataplexy may occur near the time of onset of sleepiness, but can develop significantly later in many cases. Hypnagogic and hypnopompic hallucinations as well as sleep paralysis are much less specific for narcolepsy than is cataplexy and they occur frequently in healthy control subjects (243). As time passes, symptoms of sleepiness can have significant negative effects on mood and health-related quality of life (257, 258). With aging, there is an increasing tendency to have more fragmented nocturnal sleep and some patients have developed REM sleep behavior disorder (RBD), also based on dysregulated REM sleep physiology (259, 260).

6.7. Differential Diagnosis

Recurrent hypersomnia, especially the Kleine–Levin syndrome, is rare (∼200 cases reported), more common in male individuals, with adolescent onset, and typically remitting after a few years. These spells of hypersomnia last many days with very long bouts of sleep punctuated by brief and abnormal wakeful periods that typically include hyperphagia and hypersexuality (15, 261). Hypersomnia conditions must be distinguished from behaviorally induced insufficient sleep syndrome and sleepiness caused by substances, medications, and medical disorders.

Although mood disorders are often associated with fatigue, lethargy, and/or psychomotor retardation, they are not typically associated with actual hypersomnia unless mediated by medication (262). If hypersomnia is difficult to distinguish from fatigue with depression, PSG and MSLT documentation are required (263). Other sleep disorders, such as OSA and RLS with periodic limb movement disorder, may be associated with hypersomnia. This is important, because shift work (for men), sleep restriction, antidepressant use, and possibly OSA can also be associated with SOREMPS not necessarily caused by narcolepsy (264–266). Circadian rhythm sleep disorders are associated with sleep propensity at unusual times, such as in the early evening with the advanced sleep phase type or in the morning with delayed sleep phase type. Similarly, jet lag and shift work sleep disorders can include periods of heightened sleepiness.

Secondary, or symptomatic narcolepsy caused by other brain disorders has been described in association with diencephalic and brainstem neoplasm or infarction, other diencephalic lesions, pituitary–hypothalamic disease, and multiple sclerosis. Head trauma can be associated with hypersomnia, but not typically the narcolepsy syndrome (267). Secondary narcolepsy is not associated with HLA-DQB1*0602 at rates beyond those of the general population (241).

Isolated sleep paralysis, at sleep onset or offset, may occur independently of narcolepsy. It may be accompanied by hallucinatory experience but is not associated with cataplexy. It has been noted in folklore throughout history and underlies the descriptions of the medieval European incubus and Newfoundland Old Hag nocturnal assaults characterized by partial awakening, often early in the sleep period, with a sensation of an evil presence, muscle paralysis, a feeling of suffocation, and intense fear (268).

6.8. Etiology

The etiology of classic narcolepsy with cataplexy has been attributed to the loss of neurons in the lateral hypothalamus that secrete the single peptide known both as orexin and hypocretin because it has been studied with respect to feeding as well as sleep behavior. Mouse knockout preparations and canine species bred for deficient hypocretin receptors have further clarified this pathophysiological mechanism. Onset of human narcolepsy often follows some form of stress, which may influence the damage to hypocretin-secreting cells. These stresses include head trauma, sudden sleep–wake habit changes, and infections. The presence of HLA-DQB1-0602 in serum of these patients suggests an autoimmune neuronal destruction, although the mechanism of cell loss has not yet been determined. Family studies have documented the incidence of narcolepsy in 1 to 2% of first-degree relatives of patients, a modest increase of risk, although clearly more than in the general population. Slightly more, 4 to 5%, have isolated excessive daytime sleepiness. Monozygotic twin

discordance appears in 25 to 35% of reported twin pairs, further suggesting environmental influence (269).

The etiology of idiopathic hypersomnia is not known (236). Like narcolepsy, some cases seem to follow a viral illness, such as Guillain–Barré syndrome, hepatitis, mononucleosis, or atypical viral pneumonia (237). Some cases may have familial distribution in which HLA-Cw2 and DR11 alleles may appear (270).

6.9. Treatment

Treatment of any hypersomnia must emphasize good sleep hygiene and efforts to obtain sufficient nocturnal sleep. For narcolepsy, strategic naps can be helpful, followed by variable periods of increased alertness. Such naps may be unrefreshing and followed by sleep inertia in idiopathic hypersomnia.

Pharmacological treatment is essential to support maintenance of wakefulness in narcolepsy and hypersomnolent patients. Wake-promoting drugs are very helpful although they do not entirely restore normal daytime alertness. MSLT latencies approach a maximum of approximately 50% of normal values with modafinil and approximately 65 to 75% with dextroamphetamine, methamphetamine, and methylphenidate (271). The traditional stimulant drugs act as dopamine reuptake inhibitors to enhance behavioral arousal. High doses of these agents (>120 mg methylphenidate, amphetamine, dextroamphetamine, or >100 mg methamphetamine) may be required in occasional patients, but caution is then advised in view of potential psychiatric side effects, such as psychosis, substance misuse, and psychiatric hospitalizations, as well as tachyarrhythmias and anorexia or weight loss (272). Modafinil, widely used in Europe before introduction into the United States, acts by an unknown mechanism on hypothalamic wake-promoting areas. Its half-life of elimination, 12 to 15 hours, allows for single-dosing schedules. It is also indicated for residual hypersomnia in patients treated for OSA (273). Sodium oxybate (gamma hydroxybutyrate [GHB]) has been marketed to enhance daytime alertness as well as nocturnal sleep continuity. It was originally marketed for treatment of cataplexy. It must be taken in divided doses at bedtime and again during the night, 4 hours later (274). Because it is a drug of considerable abuse potential, its use is very strictly regulated. It should be reserved for cases clearly not responsive to therapy that is more conventional. Cataplexy does not typically remit with stimulant or modafinil therapy, but responds to adjunctive REM-inhibiting drugs, such as tricyclic and SSRI antidepressants. Venlafaxine and atomoxetine have also been reportedly effective (237).

7. Parasomnias

7.1. Definition

Parasomnias are disorders marked by undesirable physical and/or experiential phenomena occurring during entry into sleep, within sleep, or during arousals from sleep. They may involve motoric and/or autonomic activation. DSM-IV-TR distinguishes nightmare disorder (formerly known as dream anxiety disorder), sleep terror disorder, sleepwalking disorder, and parasomnias not otherwise specified (1). Unfortunately, this limited categorization understates the richness of the various disorders representing, as a group, the unusual and frequently bizarre manifestations of sleep–wake state misalignment. When states of sleep and wake are incompletely separated, experiential, cognitive, behavioral, and autonomic components of one state overlap with those of the other and the consequence is an abnormal combination such as complex frenzied emotion and/or ambulation during incomplete wakefulness that can carry serious risk of injury to self or others. Any imaginable superimposition of sleep and wakeful behavior has or will appear in the medical literature.

The ICSD-2 cites disorders of arousal from non-REM sleep as distinct from parasomnias usually associated with REM sleep. The former include the prototype of their group: confusional arousals. These are recurrent, usually brief spells of apparent awakening from nocturnal or napping sleep with confusion. This is the "sleep drunkenness" of older literature and represents incomplete awakening that may include disorientation, blunted responsiveness to stimuli, and memory impairment. Two variants in adolescents and adults, severe morning sleep inertia, and sleep-related abnormal sexual behaviors are also recognized. Sleepwalking includes 1) ambulation during sleep, 2) persistence of sleep, altered consciousness, or impaired judgment and at least one of: (a) difficulty arousing the person, (b) confusion on awakening, (c) complete or partial amnesia, (d) routine behaviors occurring at inappropriate times, (e) inappropriate or nonsensical behaviors, or (f) dangerous or potentially dangerous behaviors. Sleep terrors are spells of 1) intense fear during sleep, usually initiated by a loud vocalization. These include 2) at least one of: (a) difficulty arousing the person, (b) confusion when awakened, (c) complete or partial amnesia, or (d) dangerous or potentially dangerous behaviors. 3) Both sleepwalking and sleep terrors are not better explained by any other sleep, medical, neurological, mental, substance use disorders, or medication use (15).

Parasomnias usually associated with REM sleep include REM sleep behavior disorder (RBD), recurrent isolated sleep paralysis, and nightmare disorder. Sleep paralysis, not limited to narcolepsy, is a transient 1) inability to move trunk and limbs when awakening from sleep or, in some cases, at sleep onset, lasting 2) seconds to a few minutes. This represents peripheral muscle atonia of REM sleep dissociated from normal REM sleep, and appearing or persisting at inappropriate times (15). Nightmare disorder designates 1) recurrent awakenings from sleep during very disturbing dream experiences that can include many diverse emotions, typically fear and anxiety, which are followed by 2) full alertness on awakening with clear recall of dream content. 3) There must also

be at least one of delayed return to sleep, and/or spell occurrences during the latter half of the habitual sleep period.

The quintessential REM sleep parasomnia is RBD. Diagnostic criteria include 1) polysomnographic finding of REM sleep without atonia, such as abnormal persistence of electromyographic muscle tone or excessive intermittent muscle twitching during REM sleep, and 2) at least one of a history of sleep-related behavior that is potentially or actually injurious or disruptive, or polysomnographic evidence of behaviors during REM sleep. There is also 3) absence of electroencephalographic epileptiform or clinical seizure activity during REM sleep (15).

7.2. Epidemiology

The prevalence of disorders of arousal has been estimated at 1 to 6.5% for sleep terrors, and 5 to 30% for sleepwalking in children and adolescents (275–277). It has been estimated that 2 to 5% of adults may experience sleepwalking (278–280). A large systematic telephonic survey of individuals aged 15 years and older in the United Kingdom documents sleep terrors in 2.2% (2.6% for ages 15–24 years; 1.0% for ages >65 years), sleepwalking episodes in 2.0% (4.9% for ages 15–24 years, 0.5% for ages >65 years), and confusional arousals in 4.2% (8.9% for ages 15–24 years, 1.4% for ages >65 years). In the same population, 2.0% of all respondents reported some violent behavior during sleep. The authors note the absence of chronically ill or institutionalized subjects in the general population sampled, excluding estimation of the prevalence of RBD that is found predominantly in the elderly (281).

7.3. Clinical Picture

Sleepwalking is characterized by abrupt arousals from sleep with movement from the bed that can include complex, automatic behaviors, such as wandering about, carrying objects from place to place without reason, rearranging furniture, eating inappropriately, urinating in closets, going out of doors, and, rarely, even driving an automobile (282). Eyes may be open but with glassy stare. Communication is variable, but the individual may mumble or speak nonsensically. Frenzied, aggressive behavior is possible and may involve use of weapons. The effects of suspended judgment can result in inadvertent injury or death to the sleepwalker or someone else (283, 284).

Spells of sleepwalking typically emerge during the first third of the sleep period, when non-REM sleep, particularly stages 3/4, predominate. They generally last for minutes to an hour, although with great variability. Sleep terrors typically begin with sudden, loud screaming accompanied by tachycardia, tachypnea, and mydriasis, with unresponsiveness to consolation. In some cases, frenzied motor behavior can ensue. Pure sleep terrors occur commonly in children, who return to sleep without difficulty and awaken unperturbed in the morning, in contrast to the parents, for whom the spells are most troubling. In both disorders, patients are typically amnestic for the spells. Adults with disorders of arousal often experience mixed sleepwalking and sleep terrors associated with either fragmentary or elaborate dream imagery (285, 286).

Dream enactment, or spells of oneiric behavior of RBD tend to emerge at least 90 minutes after sleep onset and especially during the latter part of the night, when REM sleep periods are of longer duration with more dense phasic eye movements. Behaviors are typically aggressive or exploratory and never appetitive (feeding, sexual). They are usually very abrupt and brief in duration. There is very active dream content, often with preceding prodromal action-packed dreaming for months or years before sleep-related behavior begins. Behavior is clearly concordant with reported dream content, which usually involves confrontation, aggression, and violence, despite usually calm and pleasant wakeful personalities. Behavioral features of the disorder are indistinguishable across sexes, ages, and presence or absence of neurological disorder (287). Recently, a video and book containing a large number of patients' descriptions of their parasomnias, along with pertinent clinical and scientific information has been published. A documentary film on the topic has been produced (285, 286, 288).

Many interesting variations of these disorders have been reported. Overlapping non-REM and REM sleep parasomnias can co-occur in the same patient (289). Sleep-related eating disorder (SRED), now recognized as a distinct parasomnia, is most often a variant of sleepwalking and includes eating rich, often thick fluids, such as milk shakes, peanut butter, or brownies, and may involve unusual substances that would not be consumed during wakefulness. It is not associated with awareness of hunger or thirst, despite a drive to eat described as "out of control." There is no associated purging and more than 40% of patients are overweight (290–292). Other associated risk factors for SRED include RLS, periodic limb movement disorder, OSA, and zolpidem use, but it is also idiopathic in many cases. Sleep-related sexual behavior can also occur during sleep and may be confused with wakeful, inappropriate conduct (293, 294, 381).

Numerous other parasomnias are included within the ICSD-2, and the reader is referred there for descriptions, including recurrent isolated sleep paralysis, sleep enuresis, sleep-related groaning, exploding head syndrome, and sleep-related hallucinations (15).

7.4. Case Histories

7.4.1. Sleepwalking/Sleep Terrors

A 28-year-old man with a history of sleepwalking from ages of 5 to 10 years begins to have nocturnal spells increasingly frequently during the 5 months after beginning a new job. He is required to begin his workday approximately 2 hours

earlier than for his former employment. Approximately three or more times weekly, within 2 to 3 hours after falling asleep, he is observed to moan or yell, and then arise to walk briskly out of the room or into a closet. These events typically last several minutes and he often pounds on the wall or floor before returning to bed and to sleep, with no recall of the experiences the following morning. He is brought to an emergency room one night after punching a bathroom window and suffering lacerations to the right hand and wrist. He recalls dreaming that some vague, darkly cloaked assailant seemed to be threatening harm, and then he awakened with a bloody hand. His fiancée later demands that he pursue psychiatric consultation, assuming that he was expressing anger during sleep rather than talking openly with his rigid supervisor at the workplace. The psychiatrist prescribes 0.5 mg clonazepam taken 20 minutes before bedtime for 1 month, during which the patient begins going to bed an hour earlier each night and practices a relaxing exercise of self hypnosis with imagery of peaceful sleep. He remains free of spells thereafter.

7.4.2. REM Sleep Behavior Disorder

For a period of 6 months, a 77-year-old man has almost nightly spells of yelling with vigorous arm and leg movements that have caused bruises to his wife. He is a mild mannered person by day, but he curses and punches violently at assailants in the visually vivid dreams that occur predominantly in the early morning hours. For many years before these behaviors emerged, he experienced action-packed dreaming with violent content. His wife can no longer share the same bed with him, so he uses a smaller bed in an adjoining room. He is brought to his physician the day after having fallen from bed, suffering a fractured wrist during a spell. He recalls dreaming that he was chasing and beating a man who had threatened him. Mental status and neurological examinations reveal no notable findings. After subsequent referral to a sleep center, he undergoes PSG revealing bursts of muscle tone and extremity movement during apparent REM sleep. He begins sleeping peacefully with no motor activation after prescription of clonazepam, initially 0.25 mg, then 0.5 mg taken 20 minutes before bedtime. He is then sent to a neurologist for long-term follow-up after a frank discussion of the possibility for future development of neurodegenerative illness.

7.5. Laboratory Findings

On PSG, there are few diagnostic markers of disorders of arousal in the absence of a spell. Bursts of slow EEG waveforms known as hypersynchronous delta activity are possible indicators of a drive to enhance depth of sleep but are not specific to these disorders (295). Actual episodes of sleepwalking or sleep terrors are often not observed during PSG. When they occur, they appear as abrupt arousals from non-REM sleep, typically but not exclusively from stages 3/4. With sleep terrors, there may be impressive tachycardia and tachypnea. Muscle activity often obscures the underlying EEG, which can demonstrate diffuse rhythmic delta activity, diffuse delta and theta activity intermixed with alpha and beta activity, and/or prominent alpha and beta activity. Hence, the EEG during episodes of disorders of arousal can show either the complete persistence of sleep, the admixture of sleep and wakefulness, or complete wakefulness despite the behavioral manifestations of a mixed state (296, 297).

Brain imaging studies are not used for clinical evaluation, although a case report with SPECT imaging during a sleepwalking spell has demonstrated cerebral blood flow (CBF) to be increased in the anterior cerebellum (vermis) and posterior cingulate cortex when compared with quiet slow wave sleep. There are also large areas of frontal and parietal cortex decrements of CBF when compared with healthy awake subjects. Sleepwalking seems to represent a concurrence of increased motor activation and decreased executive function during incomplete, disordered arousals from sleep (298) (Figs. 37.6 and Color Plate 11, following p. 650).

In the case of RBD, there is preserved normal cycling of non-REM and REM sleep stages as well as distribution of all sleep stages. The characteristically increased electromyographic muscle tone and/or extremity movement during REM sleep is usually based on the interpretation of an experienced sleep specialist (Fig. 37.7). A scoring system, however, has been proposed to quantify the degree of abnormal motor activity (299, 300). Importantly, there may be epochs of REM sleep with normal muscle atonia in a given muscle group (e.g., under the chin) concurrent with bursts of tone or movement in another group (e.g., a limb). When an actual behavioral event is observed, it is clearly related to a period of REM sleep and the laboratory technologist can subsequently ask the patient for a description of dream content, which is typically concordant with the behavior just observed (Fig. 37.7).

Neuropsychological testing, although not indicated for diagnosis, has revealed dysfunctional visuospatial constructional ability and altered visuospatial learning in early, apparently idiopathic RBD. This may be consistent with the possibility of underlying neurodegenerative disorder (301).

7.6. Clinical Course

Commonly beginning in childhood, sleepwalking peaks between 11 and 12 years of age. Sleepwalking and sleep terrors generally subside in later childhood and adolescence but may continue into, and rarely arise during, adulthood. RBD, on the other hand, usually presents in older adults, typically men. In an early series of cases followed during longer than a decade, 11 (38%) of 29 of cases initially diagnosed as idiopathic RBD evolved into a parkinsonian disorder after a mean of nearly 4 years after diagnosis of RBD and nearly 13 years after its onset (302). With time, this same cohort yielded a total of 17 (65.4%) of 26 patients developing a parkinsonian disorder or dementia without Parkinsonism (in one case) during an average of 13.3 years after

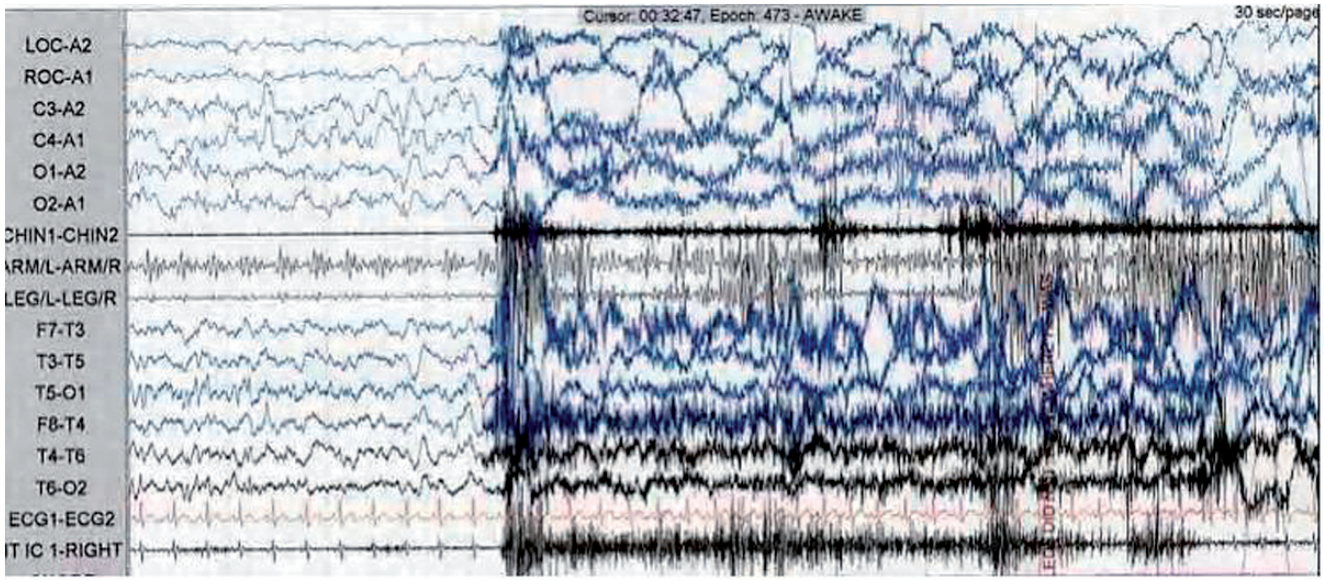

FIGURE 37.6. A 30-second epoch demonstrating an abrupt arousal from non-REM stages 3/4 sleep with subsequent movement and muscle artifact obscuring most of the underlying EEG in a patient with a history of sleepwalking. Note the absence of tachycardia, which would occur in classic sleep terrors (*see* Color Plate 11, following p. 650).

onset of RBD (303). Idiopathic RBD, in many cases, is an early herald of neurodegenerative disorders associated with deposits of alpha-synuclein, a protein component of intracellular inclusion bodies in brains of patients suffering Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy (MSA) (304). In view of this and neuropsychological deficits of impaired visuospatial constructional performance, visuospatial learning, verbal memory, executive problem solving, and/or verbal associative fluency resembling those of dementia with Lewy bodies in a number of idiopathic RBD cases, some authors have suggested that idiopathic RBD might rather be designated cryptogenic RBD (305).

Violent parasomnias, disorders of arousal, as well as RBD can be associated with very complex behavior and serious risk of injury. Cases of sleepwalking/sleep terrors have been documented to include long-distance driving (282), and, rarely, even homicide (283, 284). Spells of RBD are typically abrupt, usually of brief duration, and can yield injuries in as many as 79 to 96% of patients who enact dreams of violent content resulting in fractures and lacerations. This also causes injury to bed partners in a number of reported cases. Both disorders of arousal and RBD tend to occur independent of any psychiatric disorder (284, 306), although the former are typically more likely to occur during periods of stress and the latter have been reported in a few cases as sequelae of severe psycho-

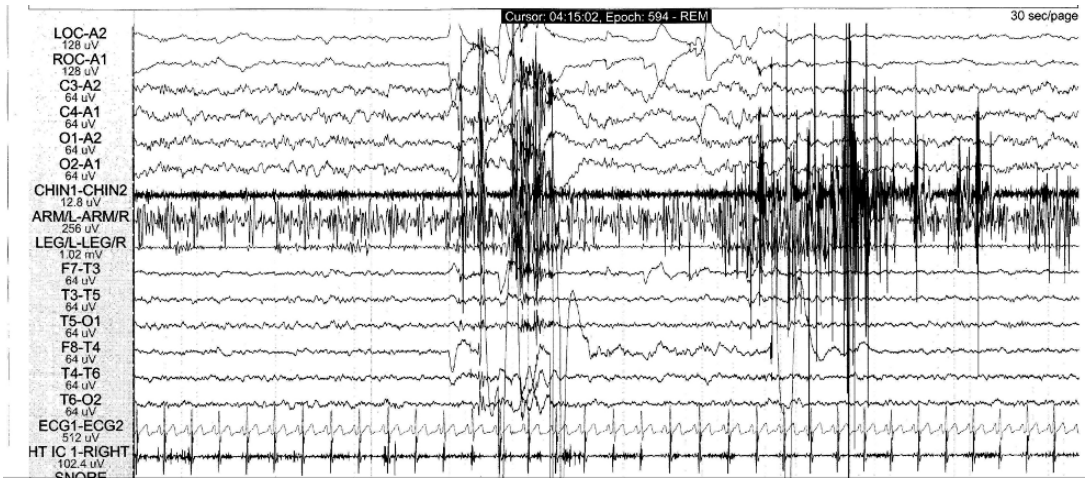

FIGURE 37.7. A 30-second epoch of REM sleep with increased tonic muscle tone in the chin EMG and bursts of phasic upper and lower extremity movement characteristic of the polysomnogram in cases of RBD.

logical stress (307, 308). A large epidemiological survey has found violent sleep-related behavior to be more frequently acknowledged in persons with DSM-IV anxiety and mood disorders or psychotic symptoms, although no etiological relationship has been clearly established with psychiatric illness (281). In another report by the same author, DSM-IV mood disorders were present in 25.8% of those reporting confusional arousals, 30.4% with sleep terrors, and 14.6% with sleepwalking. Anxiety disorders were present in 18.9% with confusional arousals, 34.2% with sleep terrors, and 12.7 with sleepwalking (309). For comparison, lifetime prevalence for major depression is 10 to 25% for women and 5 to 12% for men. Anxiety disorders have 1 to 5% lifetime prevalence (1).

7.7. Differential Diagnosis

Sleep-related seizure disorders can present as any imaginable behavioral and/or autonomic events. These have included obvious nocturnal seizures (306–316), episodic nocturnal wandering (317,318), and hypnogenic paroxysmal dystonia (a frontal lobe seizure disorder) (319, 320). Disorders of arousal and "pseudo-RBD" can be precipitated by sleep fragmentation caused by such disorders as OSA (321–325) and rhythmic movement disorders (326, 327). It is important to note that anything capable of precipitating an arousal from sleep can precipitate a disordered arousal.

Of interest to psychiatrists is nocturnal psychogenic dissociative disorder, which can resemble other parasomnias, but emerges clinically after the individual undergoes a transition from sleep to electroencephalographically determined wakefulness while appearing to remain behaviorally asleep. Most typically, these patients have DSM-IV diagnoses of daytime dissociative disorders to include borderline personality disorder. In these cases, apparently sleep-related behaviors may be self-injurious and dream-like mentation can recall past trauma. Interestingly, BZ drugs that are effective in disorders of arousals and RBD may aggravate dissociative spells (328).

Panic disorder may include nocturnal attacks that arise abruptly, most commonly during deepening non-REM sleep. Full awakening and prolonged return to sleep typically follows spells in contrast to the lack of full consciousness and prompt resumption of sleep with sleep terrors (329). Malingering remains a possibility to be kept in mind (330). Nightmares are awakenings from REM sleep with intensely discomforting dream mentation involving negative emotion of any nature. Spells are brief, and yield to full awakening without confusion or oneiric behavior. They occur commonly but not exclusively after trauma and may also occur as side effects of antidepressants, antihypertensives, dopamine receptor agonists, antihistamines, and withdrawal of REM sleep-inhibiting drugs, leading to REM sleep rebound (15).

7.8. Etiology

The neural basis for disorders of arousal has not been elucidated, but it must reside in the dysregulation of transitions from sleep to wakefulness. Previous sleep deprivation, causing increased physiological sleep propensity, seems to increase the likelihood of disordered arousal in predisposed individuals. It may even be used to facilitate induction of spells during PSG (331). Similarly, alcohol and sedating drugs also slow this transition. Sleepwalking and sleep terrors have been associated with olanzapine (332), lithium, and other neuroleptics, often in combination (333). Sleep-related eating has been associated with zolpidem (334), olanzapine (85), and risperidone (84).

RBD is the result of impaired muscle atonia, coupled with the liberation of typically aggressive and violent dream enactment during REM sleep. The animal model of RBD, based on experimentally induced pontine lesions in cats, has been known since 1965 (335). Most human RBD, however, is not clearly associated with such anatomical lesions. Because of the eventual development of Parkinson's disease, dementia, and MSA in high numbers of patients with initially idiopathic RBD (52%, 60%, and 36%, respectively, in one study), and the decreased striatal dopamine transporter protein shown in SPECT and PET scan studies, the etiology of RBD seems to be that of the neurodegenerative disorders. Therefore, as noted above, RBD seems to be a herald symptom (336–338). Numerous other neurodegenerative disorders may also be associated with RBD (339). RBD can often be attributed to REM suppressing drug use as well as withdrawal, to tricyclic antidepressants; monoamine oxidase inhibitors; cholinergic drugs, such as biperiden; SSRIs; mirtazapine (reported in patients with Parkinson's disease); excessive caffeine use; and selegiline treatment of Parkinson's disease (287, 340–344). Narcolepsy, itself a disorder of physiological organization of REM sleep, has been associated with RBD (345).

7.9. Treatment

Sleepwalking and sleep terrors are often benign and self-limiting, especially in children, and may require no treatment beyond reassurance and attention to sleep hygiene. Attention should be paid to safety features of the sleep environment, such as placement of dangerous obstacles, accessible windows and stairways, and other dangers. If falls from bed are possible, consider placing the mattress on the floor. Instruction in self-hypnosis or relaxation–mental imagery exercises has been reported to benefit children and adults with disorders of arousal (346–349). When there is risk of injury or serious disruption to household life, pharmacotherapy should be considered. BZs have traditionally been reported as effective, as have TCAs (350).

SRED tends not to respond to BZ monotherapy, as do sleepwalking and sleep terrors. Various combinations of levodopa, opioid, bupropion, trazodone, and BZ have been

reportedly helpful (290, 351). More recently, topiramate has become the treatment of choice (352, 353). In most published cases of automatic sexual behavior during sleep, or sexsomnia, clonazepam has been found to be very effective (293, 294, 381, 381).

More than 90% of RBD cases respond to 0.5 to 2.0 mg clonazepam at bedtime, and 12-year follow-up has indicated no significant trend toward tolerance or untoward effects, although patients must be cautioned regarding possible morning hangover sedation (354, 355). In the 10% of cases not responsive or fully remitted with clonazepam, 3 to 12 mg melatonin at bedtime has become a second-line agent and it may be considered as initial therapy for frail or cognitively impaired individuals for whom BZ is deemed contraindicated (356–358). Donepezil (359), pramipexole (360, 361), and some other drugs have been reportedly effective (287, 362). Generally, however, despite the strong association of RBD and parkinsonism, dopamine agonist therapy is not highly effective in contrast to the impressive benefit of clonazepam. Every patient with RBD must have a thorough neurological assessment and they should be informed of the association of RBD with neurodegenerative disorders. Regular, long-term follow-up is essential.

Nightmares have been reported to benefit from dream rehearsal therapy, a technique of cognitive restructuring by rehearsing a desired, modified dream scenario during quiet wakefulness before retiring to bed for the night (363, 364). Pharmacotherapy with cyproheptadine has been reportedly beneficial (365–368), although one group has reported it to be ineffective (369). Prazosin (370–375), guanfacine (376), and clonidine (377) have also been reportedly helpful.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text revision. Washington, DC: American Psychiatric Association; 2000.
2. Ross R, Ball W, Sullivan K, Caroff S. Sleep disturbance as the hallmark of posttraumatic stress disorder. Am J Psychiatry 1989;146(6):697–707.
3. Buysse D, Frank E, Lowe K, Cherry C, Kupfer D. Electroencephalographic sleep correlates of episode and vulnerability to recurrence in depression. Biol Psychiatry 1997;41(4):406–418.
4. Grunhaus L, Shipley J, Eiser A, et al. Shortened REM latency post-ECT is associated with rapid recurrence of depressive symptomatology. Biol Psychiatry 1994;36(4):214–222.
5. Agargun M, Kara H, Solmaz M. Sleep disturbances and suicidal behavior in patients with major depression. J Clin Psychiatry 1997;58:249–251.
6. Thase M, Simons A, Reynolds C. Abnormal electroencephalographic sleep profiles in major depression: association with response to cognitive behavior therapy. Arch Gen Psychiatry 1996;53:99–108.
7. Wehr T. Improvement of depression and triggering of mania by sleep deprivation. JAMA 1992;267(4):548–551.
8. Stickgold R. Sleep-dependent memory consolidation. Nature 2005;437:1272–1278.
9. Van Dongen H, Maislin G, Mullington J, Dinges D. Neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 2003;26(2): 117–126.
10. Hobson J. Sleep is of the brain, by the brain and for the brain. Nature 2005;437:1254–1256.
11. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects. Los Angeles, CA: Brain Information Service/Brain Research Institute; 1968.
12. Von Economo C. Sleep as a problem of localization. J Nerv Ment Dis 1930;71:249–259.
13. Moruzzi G, Magoun H. Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurol 1949; 1:455–473.
14. Saper C, Scammell T, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature 2005;437:1257–1262.
15. American Academy of Sleep Medicine. International classification of sleep disorders, 2nd ed: Diagnostic and coding manual. 2 ed. Westchester, IL: American Academy of Sleep Medicine; 2005.
16. Sateia M, Doghramji K, Hauri P, Morin C. Evaluation of chronic insomnia. Sleep 2000;23(2):1–66.
17. Ohayon J. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002;6(2):97–111.
18. Hohagen F, Rink K, Kappler C. Prevalence and treatment of insomnia in general practice: a longitudinal study. Eur Arch Psychiatry Clin Neurosci 1993;242:329–336.
19. Schramm E, Hohagen F, Kappler C, Grasshof U, Berger M. Mental comorbidity of chronic insomnia in general practice attenders using DSM-III-R. Acta Psychiatr Scand 1995;91(1): 10–17.
20. Gallup Organization. Sleep in America. In. Princeton, NJ: Gallup Organization; 1995.
21. Bixler E, Kales A, Soldatos C, Kales J, Healey S. Prevalence of sleep disorders in the Los Angeles metropolitan area. Am J Psychiatry 1979;136:1257–1262.
22. Mellinger G, Balter M, Uhlenhuth E. Insomnia and its treatment: Prevalence and correlates. Arch Gen Psychiatry 1985;42:225–232.
23. Gislason T, Reynisdottir H, Kritbjarnarson B, Benediktsdotter. Sleep habits and sleep disturbances among the elderly—an epidemiological survey. J Intern Med 1993;234:31–39.
24. Hohagen F, Kappler C, Schramm E, et al. Prevalence of insomnia in elderly general practice attenders and the current treatment modalities. Acta Psychiatr Scand 1994;90(2): 102–108.
25. Carney C, Edinger J. Identifying critical beliefs about sleep in primary insomnia. Sleep 2006;29(3):342–350.
26. Stepanski E, Zorick F, Roehrs T, et al. Daytime sleepiness in patients with chronic insomnia compared with asymptomatic control subjects. Sleep 1988;11:54–60.
27. Zammit G. Subjective ratings of the characteristics and sequelae of good and poor sleep in normals. J Clin Psychol 1988;44: 123–130.
28. Stepanski E, Koshorek G, Zorick F, Glinn M, Roehrs T, Roth T. Characteristics of individuals who do or do not seek treatment for chronic insomnia. Psychosomatics 1989;30:421–427.
29. Evans L. Sundown syndrome in institutionalized elderly. J Am Geriatric Soc 1987;35:101–108.

30. Prinz P, Vitaliano P, Vitiello M. Sleep, EEG, and mental function changes in senile dementia of the Alzheimer's type. Neurobiol Aging 1982;3:361–370.
31. Smith M, Ellgring H, Oertel W, et al. Sleep disturbances in Parkinson's disease: relationship to behavioral problems. J Am Geriatric Soc 1997;45(2):194–199.
32. Rebok G, Rovner B, Folstein M. Sleep disturbance and Alzheimer's disease: relationship to behavioral problems. Aging 1991;3(2):193–196.
33. van Hilten J, Weggeman M, van der Velda E, Kerhof G, van Dijk, JG, Roos R. Sleep, excessive daytime sleepiness and fatigue in Parkinson's disease. J Neural Transm 1993;5(3): 235–244.
34. Roehrs T, Zorick F, Sicklesteel J, et al. Age-related sleep–wake disorders at a sleep disorders center. J Am Geriatric Soc 1983;31:364–370.
35. Reynolds C, Coble P, Black R, Holyer B, Carroll R, Kupfer D. Sleep disturbances in a series of elderly patients. J Am Geriatric Soc 1980;28:164–169.
36. Littner M, Hirshkowitz M, Kramer M, et al. Practice parameters for using polysomnography to evaluate insomnia: an update. Sleep 2003;26:754–760.
37. Perlis M, Merica H, Smith M, et al. Beta EEG activity and insomnia. Sleep Med Rev 2001;5:363–374.
38. Krystal A, Edinger J, Wohlgemuth W, et al. NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes. Sleep 2002;25:630–640.
39. Bonnet M, Arand D. Insomnia, metabolic rate, and sleep restoration. J Intern Med 2003;254:23–31.
40. Littner M, Kushida C, Anderson W, et al. Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: an update for 2002. Sleep 2002;26(3): 337–341.
41. Nofzinger E, Buysse D, Germani A, Price J, Miewald J, Kupfer D. Functional neuroimaging evidence for hyperarousal in insomnia. Am J Psychiatry 2004;161:2126–2129.
42. Sateia M, Nowell P. Insomnia. Lancet 2004;364:1959–1973.
43. Silber M. Chronic insomnia. N Engl J Med 2005;353(8): 803–810.
44. Benca R. Diagnosis and treatment of chronic insomnia: a review. Psychiatric Services 2005;56(3):332–343.
45. Spielman A, Caruso L, Glovinsky P. A behavioural perspective on insomnia treatment. Psychiatr Clin North Am 1987;10: 541–553.
46. Hauri P, Olmstead E. Childhood-onset insomnia. Sleep 1980;3:59–65.
47. Regestein Q, Monk T. Delayed sleep phase syndrome: a review of its clinical aspects. Am J Psychiatry 1995;152:602–608.
48. Bastien C, Morin C. Familial incidence of insomnia. J Sleep Res 2000;9:49–54.
49. Vgontzas A, Tsigos C, Bixler E, et al. Chronic insomnia and activity of the stress system: a preliminary study. J Psychosom Res 1998;45:21–31.
50. Ford D, Kamerow D. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? JAMA 1989;262:1479–1484.
51. Chang P, Ford D, Mead L, Cooper-Patrick L, Klag M. Insomnia in young men and subsequent depression; the Johns Hopkins precursors study. Am J Epidemiol 1997;146: 105–114.
52. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biol Psychiatry 1996;39:411–418.
53. Lugaresi I, Medori R, Montagna P, et al. Fatal familial insomnia and dysautonomia with selective degeneration of thalamic nuclei. N Engl J Med 1986;315:997–1003.
54. Montagna P. Fatal familial insomnia: a model disease in sleep physiopathology. Sleep Med Rev 2005;9(5):339–353.
55. Buysse D, Reynolds C, Kupfer D, et al. Clinical diagnoses in 216 insomnia patients using the International Classification of Sleep Disorders (ICSD), DSM-IV and ICD-10 categories: a report from the APA/NIMH DSM-IV field trial. Sleep 1994;17:630–637.
56. Weyerer S, Dilling H. Prevalence and treatment of insomnia in the community: results from the Upper Bavarian Field Study. Sleep 1991;14:392–398.
57. Szuba M, Fernando A, Groh-Szuba G. Sleep abnormalities in treatment-resistant mood disorders. In: Amsterdam A, ed. Treatment Resistant Mood Disorders. Cambridge, UK: Cambridge University Press; 2001.
58. Benca R, Obermeyer W, Tisted R, et al. Sleep and psychiatric disorders: a meta-analysis. Arch Gen Psychiatry 1992;49: 651–668.
59. Germain A, Nofzinger E, Kupfer D, Buysse D. Neurobiology of non-REM sleep in depression: further evidence for hypofrontality and thalamic dysregulation. Am J Psychiatry 2004;161:1856–1863.
60. Baillargeon L, Demers L, Ladouceur R. Stimulus-control: nonpharmacologic treatment for insomnia. Can Fam Physician 1998;44:73–79.
61. Bootzin R, Epstein D, Wood J. Stimulus control instructions. In: Hauri P, ed. Case studies in insomnia. New York: Plenum Medical Book; 1991:19–28.
62. Spielman A, Saskin P, Thorpy M. Treatment of chronic insomnia by restriction of time in bed. Sleep 1987;10:45–56.
63. Morin C, Hauri P, Espie C, Spielman A, Buysse D, Bootzin R. Nonpharmacologic treatment of chronic insomnia: an American Academy of Sleep Medicine review. Sleep 1999;22: 1134–1156.
64. Hauri P. Sleep hygiene, relaxation therapy, and cognitive interventions. In: Hauri P, ed. Case Studies in Insomnia. New York: Plenum Medical Book; 1991:65–84.
65. Summers M, Crisostomo M, Stepanski E. Recent developments in the classification, evaluation, and treatment of insomnia. Chest 2006;130(1):276–286.
66. Murtagh D, Greenwood K. Identifying effective psychological treatments for insomnia: a meta-analysis. J Consult Clin Psychol 1995;63:79–89.
67. Espie C, Inglis S, Tessier S, Harvey L. The clinical effectiveness of cognitive behaviour therapy for chronic insomnia: implementation and evaluation of a sleep clinic in general medical practice. Behav Res Ther 2001;39:45–60.
68. Edinger J, Wohlgemuth W, Radtke R, Marsh G, Quillian R. Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. JAMA 2001; 285:1856–1864.
69. Jacobs G, Pace-Schott E, Stickgold R, Otto M. Cognitive behavior therapy and pharmacotherapy for insomnia: a randomized controlled trial and direct comparison. Arch Int Med 2004;164:1888–1896.

70. Smith J, Perlis M, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry 2002;159:5–11.
71. Hauri P. Can we mix behavioral therapy with hypnotics when treating insomniacs? Sleep 1997;20:1111–1118.
72. Parrino L, Terzano M. Polysomnographic effects of hypnotic drugs, a review. Psychopharmacology (Berl) 1996;126:1–16.
73. Kryger M, Steljes D, Pouliot H, Neufeld H, Odynski T. Subjective versus objective evaluation of hypnotic efficacy: experience with zolpidem. Sleep 1991;14(5):399–407.
74. Nowell P, Mazumdar S, Buysse D, Dew M, Reynolds C, Kupfer D. Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. JAMA 1997;278:2170–2177.
75. Holbrook A, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. CMAJ 2000;162:225–233.
76. Krystal A, Walsh J, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study of adults with chronic insomnia. Sleep 2003;26:793–799.
77. Voshaar R, van Balkom A, Zitman F. Zolpidem is not superior to temazepam with respect to rebound insomnia: a controlled study. Eur Neuropsychopharmachol 2004;14:301–306.
78. Vogel G, Morris D. The effects of estazolam on sleep, performance, and memory: a long-term sleep laboratory study of elderly insomniacs. J Clin Pharmacol 1992;32:647–651.
79. Roth T, Roehrs T. A review of the safety profiles of benzodiazepine hypnotics. J Clin Psychiatry 1991;52(Suppl):38–41.
80. Rothschild A. Disinhibition, amnestic reactions, and other adverse reactions secondary to triazolam: a review of the literature. J Clin Psychiatry 1992;53(suppl):69–79.
81. Roth T, Hartse K, Saab P, Piccione P, Kramer M. The effects of flurazepam, lorazepam, and triazolam on sleep and memory. Psychopharmacology (Berl) 1980;70:231–237.
82. Canaday B. Amnesia possibly associated with zolpidem administration. Pharmacotherapy 1996;16:687–689.
83. Morgenthaler T, Silber M. Amnestic sleep-related eating disorder associated with zolpidem. Sleep Med 2002;3:323–327.
84. Lu M, Shen W. Sleep-related eating disorder induced by risperidone. J Clin Psychiatry 2004;65(2):273–274.
85. Paquet V, Strul J, Servais L, Pele I, Fossion P. Sleep-related eating disorder induced by olanzapine. J Clin Psychiatry 2002; 63(7):597.
86. Mendelson W. Effects of flurazepam and zolpidem on the perception of sleep in insomniacs. Sleep 1995;18(2):92–96.
87. Erman M, Seiden D, Zammit G, Sainati S, Zhang J. An efficacy, safety, and dose-response study of ramelteon in patients with chronic primary insomnia. Sleep Med 2006;7(1):17–24.
88. Roth T, Seiden D, Sainati S, Wang-Weigand S, Zhang J, Zee P. Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. Sleep Med 2006;7(4):312–318.
89. Hirai K, Kita M, Ohta H, et al. Ramelteon (TAK-375) accelerates reentrainment of circadian rhythm after a phase advance of the light-dark cycle in rats. J Biol Rhythms 2005;20(1):27–37.
90. Walsh J. Drugs used to treat insomnia in 2002: Regulatory-based rather than evidence based medicine. Sleep 2004;27(8): 1441–1442.
91. Woods J, Katz J, Winger G. Benzodiazepines: use, abuse, and consequences. Pharm Rev 1992;44:151–347.
92. Golden R, Dawkins K, Nicholas L. Trazodone and nefazodone. In: Schatzberg A, Nemeroff C, eds. The American Psychiatric Textbook of Psychopharmacology, 3rd ed. Washington, DC: American Psychiatric Publishing; 2004:315–325.
93. Parrino L, Spaggiari M, Boselli M, et al. Clinical and polysomnographic effects of trazodone CR in chronic insomnia associated with dysthymia. Psychopharmacology (Berl) 1994;116:389–395.
94. Saletu-Zyhlarz G, Abu-Bakr M, Anderer P, et al. Insomnia in depression: differences in objective and subjective sleep awakening quality to normal controls and acute effects of trazodone. Prog Neuropsychopharmacol Biol Psychiatry 2002;26: 249–260.
95. van Bemmel A, Havermans R, van Diest R. Effects of trazodone on EEG sleep and clinical state in major depression. Psychopharmacology (Berl) 1992;107:569–574.
96. Walsh J, Erman M, Erwin C, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSM-III-R primary insomnia. Hum Psychopharmacol 1998;13:191–198.
97. Buysse D, Germain A, Moul D, Nofzinger E. Insomnia. In: Buysse D, ed. Sleep Disorders in Psychiatry. Washington, DC: American Psychiatric Publishing; 2005:29–75.
98. Hendrickse W, Roffwarg H, Grannemann B, et al. The effects of fluoxetine on the polysomnogram of depressed outpatients: a pilot study. Neuropsychopharmacology 1994;10(2):85–91.
99. Kerkhofs M, Rielaert C, de Maertelaer V, Linkowski P, Czarka M, Mendlewicz J. Fluoxetine in major depression: efficacy, safety and effects on sleep polygraphic variables. Int Clin Psychopharmacol 1990;5(4):253–260.
100. Rush A, Armitage R, Gilin J, et al. Comparative effects of nefazodone and fluoxetine on sleep; in outpatients with major depressive disorder. Biol Psychiatry 1998;44:3–14.
101. Schenck C, Mahowald M, Kim S, O'Connor K, Hurwitz T. Prominent eye movements during NREM sleep and REM sleep behavior disorder associated with fluoxetine treatment of depression and obsessive–compulsive disorder. Sleep 1992;15(3):226–235.
102. Nelson J. Tricyclic and tetracyclic drugs. In: Schatzberg A, Nemeroff C, eds. The American Psychiatric Publishing Textbook of Psychopharmacology, 3d ed. Washington, DC: American Psychiatric Publishing; 2004:207–230.
103. Feuillade P, Pringuey D, Belugou J. Trimipramine: acute and lasting effects on sleep in healthy and major depressive subjects. J Affect Disord 1992;24:135–145.
104. Roth T, Zorick F, Wittig R, et al. The effects of doxepin HCl on sleep and depression. J Clin Psychiatry 1982;43: 366–368.
105. Shipley J, Kupfer D, Griffin S, et al. Comparison of effects of desipramine and amitriptyline on EEG sleep of depressed patients. Psychopharmacology (Berl) 1985;85:14–22.
106. Hajak G, Rodenbeck A, Voderholzer U, et al. Doxepin in the treatment of primary insomnia: a placebo-controlled, double-blind, polysomnographic study. J Clin Pychiatry 2001;62: 453–463.
107. Hohagen F, Montero R, Weiss E, et al. Treatment of primary insomnia with trimipramine: an alternative to benzodiazepine hypnotics? Eur Arch Psychiatry Clin Neurosci 1994;244: 65–72.
108. Flores B, Schatzberg A. Mirtazapine. In: Schatzberg A, Nemeroff C, eds. The American Psychiatric Publishing Text-

book of Psychopharmacology, 3rd ed. Washington, DC: American Psychiatric Publishing; 2004:341–347.
109. Ruigt G, Kemp B, Groenhout C, et al. Effect of the antidepressant Org 3770 on human sleep. Eur J Clin Parmacol 1990;38:551–554.
110. Winokur A, Sateia M, Hayes J, et al. Acute effects of mirtazapine on sleep continuity and sleep architecture in depressed patients: a pilot study. Biol Psychiatry 2000;48:75–78.
111. Kudo Y, Kurihara M. Clinical evaluation of diphenhydramine hydrochloride for the treatment of insomnia in psychiatric patients: a double-blind study. J Clin Psychiatry 1990;30: 1041–1048.
112. Meuleman J, Nelson R, Clark R. Evaluation of temazepam and diphenhydramine as hypnotics in a nursing home population. Drug Intell Clin Pharm 1987;21:716–720.
113. Rickels K, Morris R, Newman H, et al. Diphenhydramine in insomniac family practice patients: a double-blind study. J Clin Pharmacol 1983;23:234–242.
114. Richardson G, Roehrs T, Rosenthal L, et al. Tolerance to daytime sedative effects of H1 antihistamines. J Clin Psychopharmacol 2002;22:511–515.
115. Wetter T, Lauer C, Gillich G, Pollmacher T. The electroencephalographic sleep pattern in schizophrenic patients treated with clozapine or classical antipsychotic drugs. J Psychiat Res 1996;30(6):411–419.
116. Lee J, Woo J, Meltzer H. Effects of clozapine on sleep measures and sleep-associated changes in growth hormone and cortisol in patients with schizophrenia. Psychiatry Res 2001;103: 157–166.
117. Armitage R, Cole D, Supes T, Ozcan M. Effects of clozapine on sleep in bipolar and schizoaffective disorders. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:1065–1070.
118. Cohrs S, Rodenbeck A, Guan Z, et al. Sleep-promoting properties of quetiapine in healthy subjects. Psychopharmacology (Berl) 2004;174:421–429.
119. Sharpley A, Attenburrow M, Hafizi S, Cowen P. Olanzapine increases slow-wave sleep and sleep continuity in SSRI-resistant depressed patients. J Clin Psychiatry 2005;66(4): 450–454.
120. Sharpley A, Vassallo C, Cowen P. Olanzapine increases slow-wave sleep: evidence for blockade of central 5-HT2C receptors in vivo. Biol Psychiatry 2000;47:468–470.
121. Sharpley A, Bhagwagar Z, Hafizi S, Whale W, Gijsman H, Cowen P. Risperidone augmentation decreases rapid eye movement sleep and decreases wake in treatment-resistant depressed patients. J Clin Psychiatry 2003;64(2):192–196.
122. Ekbom K. Restless legs syndrome. Neurology 1960;10: 868–873.
123. Allen R, Earley C. Restless legs syndrome: a review of clinical and pathophysiologic features. J Clin Neurophysiol 2001;18:128–147.
124. Lavigne G, Montplaisir J. Restless legs syndrome and sleep bruxism: prevalence and association among Canadians. Sleep 1994;17:739–743.
125. Nichols D, Allen R, Grauke J, et al. Restless legs syndrome symptoms in primary care: a prevalence study. Arch Int Med 2003;163:2323–2329.
126. Phillips B, Young T, Finn L, Asher K, Hening W, Purvis C. Epidemiology of restless legs symptoms in adults. Arch Int Med 2000;160:2137–2141.
127. Rothdach A, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Neurology 2000;54:1064–1068.
128. Goodman J, Brodie C, Ayida G. Restless leg syndrome in pregnancy. BMJ 1988;297:1101–1102.
129. Lee K, Zaffke M, Baratte-Beebe K. Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. J Womens Health Gend Based Med 2001;10:335–341.
130. Hui D, Wong T, Ko F, et al. Prevalence of sleep disturbances in Chinese patients with end-stage renal failure on continuous ambulatory peritoneal dialysis. Am J Kidney Dis 2000;36: 783–788.
131. Winkelman J, Chertow G, Lazarus J. Restless legs syndrome in end-stage renal disease. Am J Kidney Dis 1996;28:372–378.
132. Rutkove S, Matheson J, Logigian E. Restless legs syndrome in patients with polyneuropathy. Muscle Nerve 1996;19:670–672.
133. Earley C. Restless legs syndrome. N Engl J Med 2003;348: 2103–2109.
134. Silber M, Ehrenburg B, Allen R, et al. An algorithm for the management of restless legs syndrome. Mayo Clin Proc 2004;79(7):916–922.
135. O'Keefe S, Gavin K, Lavan J. Iron status and restless legs syndrome in the elderly. Age Ageing 1994;23:200–203.
136. Silber M. Calming restless legs (editorial). Sleep 2004;27(5):839–841.
137. Sun E, Chen C, Ho G, Earley C, Allen R. Iron and the restless legs syndrome. Sleep 1998;21:371–377.
138. Ulfberg J, Nystrom B. Restless legs syndrome in blood donors. Sleep Med 2004;5(2):115–118.
139. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P. Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 1997;12: 61–65.
140. Montplaisir J, Boucher S, Nicholas L, et al. Immobilization tests and periodic leg movements in sleep for the diagnosis of restless leg syndrome. Mov Disord 1998;13(2):324–329.
141. Kazenwadel J, Pollmacher T, Trenkwalder C, et al. New actigraphic assessment method for periodic leg movements (PLM). Sleep 1995;18(8):689–697.
142. Kotagal S, Silber M. Childhood-onset restless legs syndrome. Ann Neurol 2004;56:803–807.
143. Walters A. Is there a subpopulation of children with growing pains who really have restless legs syndrome? A review of the literature. Sleep Med 2002;3:93–98.
144. Walters A. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. Mov Disord 1995;10:634–642.
145. Connor J, Boyer P, Menzies S, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology 2003;61:304–309.
146. Earley C, Connor J, Beard J, et al. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology 2000;54:1698–1700.
147. Michaud M, Soucy J, Chabli A, et al. SPECT imaging of striatal pre- and postsynaptic dopaminergic status in restless legs syndrome with periodic leg movements in sleep. J Neurol 2002;249:164–170.
148. Staedt J, Stoppe G, Kogler A, et al. Nocturnal myoclonus syndrome (periodic movements in sleep) related to central

dopamine D2-receptor alteration. Eur Arch Psychiatry Clin Neurosci 1995;245:8–10.
149. Turjanski N, Lees A, Brooks D. Striatal dopaminergic function in restless legs syndrome: 18F-dopa and 11C-raclopride PET studies. Neurology 1999;52:932–937.
150. Nofzinger E, Fasieczka A, Berman S, Thase M. Bupropion SR reduces periodic limb movements associated with arousals from sleep in depressed patients with periodic limb movement disorder. J Clin Psychiatry 2000;61:858–862.
151. Allen R, Becker PM, Bogan R, Schmidt M, Kushida CA, Fry JM, Poceta JS, Winslow D. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. Sleep. 2004 Aug 1;27(5): 907–914.
152. Bogan RK, Fry JM, Schmidt MH, Carson SW, Ritchie SY; TREAT RLS US Study Group. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. Mayo Clin Proc 2006;81(1):17–27.
153. Partinen M, Hirvonen K, Jama L, Alakuijala A, Hublin C, Tamminen I, Koester J, Reess J. Efficacy and safety of pramipexole in idiopathic restless legs syndrome: a polysomnographic dose-finding study—the PRELUDE study. Sleep Med. 2006; 7(5):407–417.
154. Saletu B, Gruber G, Saletu M, Brandstatter N, Hauer C, Prause W, Ritter K, Saletu-Zyhlarz G. Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole. 1. Findings on objective and subjective sleep and awakening quality. Neuropsychobiology 2000;41(4):181–189.
155. Dodd M, Klos K, Bower J, Geda Y, Josephs K, Ahlskog J. Pathological gambling caused by drugs used to treat Parkinson disease. Arch Neurol 2005;62(9):1377–1381.
156. Grosset K, Macphee G, Pal G, et al. Problematic gambling on dopamine agonists: not such a rarity. Mov Disord 2006;21(12):2206–2208.
157. Weintraub D, Siderowf A, Potenza M, et al. Association of dopamine agonist use with impulse control disorders in Parkinson disease. Arch Neurol 2006;63(7):969–973.
158. Ondo W. Methadone for refractory restless legs syndrome. Mov Disord 2005;20(3):345–348.
159. Caples S, Gami A, Somers V. Obstructive sleep apnea. Ann Intern Med 2005;142:187–197.
160. White D. Pathogenesis of obstructive sleep apnea. Am J Respir Crit Care Med 2005;172:1363–1370.
161. Katz I, Stradling J, Slutsky A, Hoffstein V. Do patients with obstructive sleep apnea have thick necks? Am Rev Respir Dis 1990;141(5 Pt 1):1228–1231.
162. Sharma S, Kurian S, Malik V, et al. A stepped approach for prediction of obstructive sleep apnea in overtly asymptomatic obese subjects: a hospital based study. Sleep Medicine 2004;5(4):351–357.
163. Gottlieb D, Yao Q, Redline S, Ali T, Mahowald M. Does snoring predict sleepiness independently of apnea and hypopnea frequency? Am J Respir Crit Care Med 2000;162: 1512–1517.
164. Johns M. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14:540–545.
165. Johns M. Sleepiness in different situations as measured by the Epworth Sleepiness Scale. Sleep 1994;17:703–710.
166. Gottlieb D, Whitney C, Bonekat W, et al. Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. Am J Respir Crit Care Med 1999;159:502–507.
167. Arand D, Bonnet M, Hurwitz T, Mitler M, Rosa R, Sangal B. The clinical use of the MSLT and MWT. Sleep 2005;28(1): 123–144.
168. Barbe, Pericas J, Munoz A, Findley L. Automobile accidents in patients with sleep apnea syndrome. An epidemiological and mechanistic study. Am J Respir Crit Care Med 1998;158: 18–22.
169. George C. Driving and automobile crashes in patients with obstructive sleep apnea/hypopnea syndrome. Thorax 2004; 59(9):804–807.
170. Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. N Engl J Med 1999;340:847–851.
171. Engleman H, Joffe D. Neuropsychological function in obstructive sleep apnea. Sleep Medicine Reviews 1999;3(1):59–78.
172. Findley L, Fabrizio M, Knight H, et al. Driving simulator performance in patients with sleep apnea. Am Rev Respir Dis 1989;140:529–530.
173. Flemons W, Remmers J, Whitelaw W. The correlation of a computer simulated driving program with polysomnographic indices and neuropsychological tests in consecutively referred patients for assessment of sleep apnea. Sleep 1993;16(Suppl):S71.
174. George C, Boudreau A, Smiley A. Simulated driving performance in patients with obstructive sleep apnea. Am J Respir Crit Care Med 1996;154:175–181.
175. Haraldsson P, Carenfelt C, Laurell H, et al. Driving vigilance simulator test. Acta Otolaryngol (Stockh) 1990;110: 136–140.
176. Maycock G. Sleepiness and driving; the experience of UK car drivers. J Sleep Res 1996;5:229–237.
177. Young T, Blustein J, Finn L, et al. Sleep-disordered breathing and motor vehicle accidents in a population-based sample of employed adults. Sleep 1997;21:608–613.
178. Netzer N, Stoohs R, Netzer C, Clark K, Strohl K. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Am J Respir Crit Care Med 1999;131: 485–491.
179. Ohayon M. The effects of breathing-related sleep disorders on mood disturbances in the general population. J Clin Psychiatry 2003;64(10):1195–1200.
180. Peppard P, Szklo-Coxe M, Hla M, Young T. Longitudinal association of sleep-related breathing disorder and depression. Arch Intern Med 2006;166:1709–1715.
181. Sharafkhaneh A, Giray H, Richardson P, Young T, Hirshkowitz M. Association of psychiatric disorders and sleep apnea in a large cohort. Sleep 2005;28(11):1405–1411.
182. Bardwell W, Ancoli-Israel S, Dimsdale J. Comparison of the effects of depressive symptoms and apnea severity on fatigue in patients with obstructive sleep apnea: a replication study. J Affect Disord 2007;97(1–3):181–186.
183. Bardwell W, Moore P, Ancoli-Israel S, Dimsdale J. Fatigue in obstructive sleep apnea: driven by depressive symptoms instead of apnea severity. Am J Psychiatry 2003;160(2):350–355.
184. Schroder C, O'Hara R. Depression and obstructive sleep apnea (OSA). Ann Gen Psychiatry 2005;4:13.

185. Kawahara S, Akashiba T, Akahoshi T, Horie T. Nasal CPAP improves the quality of life and lessens the depressive symptoms in patients with obstructive sleep apnea syndrome. Intern Meed 2005;44(5):422–427.
186. Li H, Huang Y, Chen N, Fang T, Liu C, Wang P. Mood improvement after surgery for obstructive sleep apnea. Laryngoscope 2004;114(6):1098–1102.
187. Means M, Lichstein K, Edinger J, et al. Changes in depressive symptoms after continuous positive airway pressure treatment for obstructive sleep apnea. Sleep Breath 2003;7(1):31–42.
188. El-Ad B, Lavie P. Effect of sleep apnea on cognition and mood. Int Rev Psychiatry 2005;17(4):277–282.
189. Verstraeten E, Cluydts R. Executive control of attention in sleep apnea patients: theoretical concepts and methodological considerations. Sleep Med Rev 2004;8(4):257–267.
190. Verstraeten E, Cluydts R, Pevernagie D, Hoffman G. Executive function in sleep apnea: controlling for attentional capacity in assessing executive attention. Sleep 2004;27(4):685–693.
191. Beebe D, Groesz L, Wells M, Nichnols B, McGee K. The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. Sleep 2003;26(3):298–307.
192. Bixler E, Vgontzas A, Lin H, et al. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med 2001;163:608–613.
193. Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med 2001;163:685–689.
194. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–1235.
195. Young T, Peppard P, Gottlieb D. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217–1239.
196. Chesson A, Berry R, Pack A. Practice parameters for the use of portable monitoring devices in the investigation of suspected obstructive sleep apnea in adults. Sleep 2003;26(7): 907–913.
197. Pittman S, Ayas N, MacDonald M, Malhotra A, Fogel R, White D. Using a wrist-worn device based on peripheral arterial tonometry to diagnose obstructive sleep apnea: in-laboratory and ambulatory validation. Sleep 2004;27(1): 923–933.
198. Hoselet J, Ayappa I, Norman R, Krieger A, Rapoport D, et al. Classification of sleep-disordered breathing. Am J Respir Crit Care Med 2001;163:398–404.
199. Guilleminault C, Kirisoglu C, Poyares D, et al. Upper airway resistance syndrome: a long-term outcome study. J Psychiatr Res 2006;40(3):273–279.
200. Brooks L. Obstructive sleep apnea syndrome in infants and children: clinical features and pathophysiology. In: Sheldon S, Ferber R, Kryger M, eds. Principles and Practice of Pediatric Sleep Medicine. Elsevier; 2005:223–229.
201. Young T. Sleep-disordered breathing in older adults: is it a condition distinct from that in middle-aged adults? [Editorial]. Sleep 1996;19:529–530.
202. He J, Kryger M, Zorick F, Conway W, Roth T. Mortality and apnea index in obstructive sleep apnea. Experience in 385 male patients. Chest 1988;94(1):9–14.
203. Narkiewicz K, Montano N, Cogliati C, van de Borne P, Dyken M, Somers V. Altered cardiovascular variability in obstructive sleep apnea. Circulation 1998;98:1071–1077.
204. Phillips B, Narkiewicz K, Pesek C, Haynes W, Dyken M, Somers V. Effects of obstructive sleep apnea on endothelin-1 and blood pressure. J Hypertens 1999;17:61–66.
205. Schulz R, Schmidt D, Blum A, et al. Decreased plasma levels of nitric oxide derivatives in obstructive sleep apnoea: response to CPAP therapy. Thorax 2000;55:1046–1051.
206. Peppard P, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378–1384.
207. Javaheri S, Parker T, Liming J, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. Circulation 1998;97:2154–2159.
208. Kaneko Y, Floras J, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med 2003;348: 1233–1241.
209. Gami A, Pressman G, Caples S, et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation 2004;110: 364–367.
210. Phillips B, Kato M, Narkiewicz K, Choe I, Somers V. Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. Am J Physiol Heart Circ Physiol 2000;279:H234–237.
211. Punjabi M, Sorkin J, Katzel L, Goldberg A, Schwartz A, Smith P. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 2002;165:677–682.
212. Smith P, Gold A, Meyers D, Haponik E, Bleecker E. Weight loss in mildly to moderately obese patients with obstructive sleep apnea. Ann Intern Med 1985;103:850–855.
213. Sullivan C, Issa F, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981;1:862–865.
214. Ballester E, Badia J, Hernandez L, et al. Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999;159:495–501.
215. Jenkinson D, Davies J, Mullins R, Stradling J. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. Lancet 1999;353:2100–2105.
216. Becker H, Jerrentrup A, Ploch T, et al. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. Circulation 2003;107: 68–73.
217. Pepperell J, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet 2002;359: 204–210.
218. Ip M, Lam B, Chan L, et al. Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive pressure. Am J Respir Crit Care Med 2000;162:2166–2171.
219. Brooks B, Cistulli P, Borkman M, et al. Obstructive sleep apnea in obese noninsulin-dependent diabetic patients: effect

of continuous positive airway pressure treatment on insulin responsiveness. J Clin Endocrinol Metab 1994;79:1681–1685.
220. Harsch I, Schahin S, Radespiel-Troger M, et al. Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2004;169:156–162.
221. Chin K, Shimizu K, Nakamura T, et al. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. Circulation 1999;100: 706–712.
222. Mansfield D, Gollogly N, Kaye D, Richardson M, Bergin P, Naughton M. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. Am J Respir Crit Care Med 2004;169:361–366.
223. Kanagala R, Murali N, Friedman P, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation 2003;107:2589–2594.
224. Gay P, Weaver T, Loube D, et al. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep 2006;29(3):381–401.
225. Edinger J, Radtke R. Use of in vivo desensitization to treat a patient's claustrophobic response to nasal CPAP. Sleep 1993;16(7):678–680.
226. Sher A, Schechtman K, Piccirillo J. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. Sleep 1996;19(2):156–177.
227. Kezirian E, Goldberg A. Hypopharyngeal surgery in obstructive sleep apnea: an evidence-based medicine review. Arch Otolaryngol Head Neck Surg 2006;132(2):206–213.
228. Li K. Surgical therapy for adult obstructive sleep apnea. Sleep Med Rev 2005;9(3):201–209.
229. Riley R, Powell N, Li K, Troell R, Guilleminault C. Surgery and obstructive sleep apnea: long-term clinical outcomes. Otolaryngol Head Neck Surg 2000;122(3):415–421.
230. Schwartz J, Hirshkowitz M, Erman M, Schmidt-Nowara W. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. Chest 2003;124:2192–2199.
231. Black J, Silber M, Krahn L, et al. Analysis of hypocretin (orexin) antibodies in patients with narcolepsy. Sleep 2005; 28(4):427–431.
232. Ohayon M, Priest R, Zulley J, Smirne S, Paiva T. Prevalence of narcolepsy symptomatology and diagnosis in the European general population. Neurology 2002;58(12):1826–1833.
233. Peled R, Lavie P. Narcolepsy-cataplexy: an extremely rare disorder in Israel (abstract). Sleep Res 1987;16:404.
234. Honda Y. Census of narcolepsy, cataplexy and sleep life among teen-agers in Fujisawa City (abstract). Sleep Res 1979; 1979:191.
235. Silber M, Krahn L, Olson E, Pankratz V. The epidemiology of narcolepsy in Olmsted County, Minnesota: a population-based study. Sleep 2002;25(2):197–202.
236. Billiard M, Dauvilliers Y. Idiopathic hypersomnia. Sleep Med Rev 2001;5(5):351–360.
237. Black J, Nishino S, Brooks S. Narcolepsy and syndromes of central nervous system-mediated sleepiness. In: Buysse D, ed. Sleep Disorders and Psychiatry Washington, DC: American Psychiatric Publishing; 2005:107–137.
238. Roth B, Nevsimalova S, Rechtschaffen A. Hypersomnia with "sleep drunkenness." Arch Gen Psychiatry 1972;26:456–462.
239. Gélineau J. De La Narcolepsie. Lancette Fr 1880;53:626–628.
240. Krahn L, Lymp J, Moore W, Slocum N, Silber M. Characterizing the emotions that trigger cataplexy. J Neuropsychiatry Clin Neurosci 2005;17:45–50.
241. Krahn L, Black J, Silber M. Narcolepsy: new understanding of irresistible sleep. Mayo Clin Proc 2001;76:185–194.
242. Yoss R, Daly D. Criteria for the diagnosis of the narcoleptic syndrome. Proc Staff Meet Mayo Clin 1957;32:320–328.
243. Guilleminault C, Fromherz. Narcolepsy: diagnosis and management. In: Kryger M, Roth T, Dement W, eds. Principles and Practice of Sleep Medicine, 4th ed. Philadelphia: Elsevier Saunders; 2005:780–790.
244. Simon D, Nishino S, Scammell T. Mistaken diagnosis of psychogenic gait disorder in a man with status cataplecticus ("limp man syndrome"). Mov Disord 2004;19(7):838–840.
245. Bhat S, Galang R. Narcolepsy presenting as schizophrenia. Am J Psychiatry 2002;159(7):1245.
246. Kryger M, Walid R, Manfreda J. Diagnoses received by narcolepsy patients in the year prior to diagnosis by a sleep specialist. Sleep 2002;25(1):36–41.
247. Douglass A. Narcolepsy: differential diagnosis or etiology in some cases of bipolar disorder and schizophrenia. CNS Spectr 2003;8(2):120–126.
248. Littner M, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. Sleep 2005;28(1):113–121.
249. Sadeh A, Hauri P, Kripke D, Lavie P. The role of actigraphy in the evaluation of sleep disorders. Sleep 1995;18:288–302.
250. Bitsios P, Schiza S, Giakoumaki S, Savidou K, Alegakis A, Siafakas N. Pupil miosis within 5 minutes in darkness is a valid and sensitive quantitative measure of alertness: application in daytime sleepiness associated with sleep apnea. Sleep 2006;29(11):1482–1488.
251. Yoss R, Moyer N, Ogle K. The pupillogram and narcolepsy: a method to measure decreased levels of wakefulness. Neurology 1969;19:921–928.
252. Mignot E, Hayduk R, Black J, Grumet F, Guilleminault C. HLA DQB1*0602 is associated with cataplexy in 509 narcoleptic patients. Sleep 1997;20:1012–1020.
253. Pelin Z, Guilleminault C, Risch N, Grumet F, Mignot E, Group UMiNMS. HLA-DQB1*0602 homozygosity increases relative risk for narcolepsy but not disease severity in two ethnic groups. Tissue Antigens 1998;51:96–100.
254. Krahn L, Pankratz V, Oliver L, Boeve B, Silber M. Hypocretin (orexin) levels in cerebrospinal fluid of patients with narcolepsy: relationship to cataplexy and HLA DQB1*0602 statue. Sleep 2002;25(7):733–736.
255. Nishino S, Kanbayashi T. Symptomatic narcolepsy, cataplexy and hypersomnia, and their implications in the hypothalamic hypocretin/orexin system. Sleep Med Rev 2005;9(4):269–310.
256. Morrish E, King M, Smith I, Shneerson J. Factors associated with a delay in the diagnosis of narcolepsy. Sleep Med 2004;5:37–41.
257. Ervik S, Abdelnoor M, Heier M, Ramberg M, Strand G. Health-related quality of life in narcolepsy. Acta Neurol Scand 2006;114(3):198–204.
258. Haba-Rubio J. Psychiatric aspects of organic sleep disorders. Dialogues Clin Neurosci 2005;7(4):335–346.
259. Billiard M, Besset A, Cadilhac J. The clinical and polygraphic development of narcolepsy. In: Guilleminault C, Lugaresi E,

eds. Sleep/Wake Disorders: Natural History, Epidemiology, and Long-term Evolution. New York: Raven Press; 1983: 171–185.
260. Schenck C, Mahowald M. Motor dyscontrol in narcolepsy: rapid-eye-movement (REM) sleep without atonia and REM sleep behavior disorder. Ann Neurol 1992;32:3–10.
261. Arnulf I, Zeitzer J, File J, Farber N, Mignot E. Kleine-Levin syndrome: a systematic review of 186 cases in the literature. Brain 2005;128(12):2763–2776.
262. Nofzinger E, Thase M, Reynolds C, et al. Hypersomnia in bipolar depression: a comparison with narcolepsy using the multiple sleep latency test. Am J Psychiatry 1991;148(9): 1177–1181.
263. Billiard M, Dolenc L, Aldaz C, Ondze B, Besset A. Hypersomnia associated with mood disorders: a new perspective. J Psychosom Res 1994;38(Suppl 1):41–47.
264. Aldrich M, Chervin R, Malow B. Value of the multiple sleep latency test (MSLT) for the diagnosis of narcolepsy. Sleep 1997;20(8):620–629.
265. Mignot E, Lin L, Finn L, et al. Correlates of sleep-onset REM periods during the multiple sleep latency test in community adults. Brain 2006;129(6):1609–1623.
266. Singh M, Drake C, Roth T. The prevalence of multiple sleep-onset REM periods in a population-based sample. Sleep 2006;29(7):890–895.
267. Malik S, Boeve B, Krahn L, Silber M. Narcolepsy associated with other central nervous system disorders. Neurology 2001;57:539–541.
268. Hufford D. The Terror that Comes in the Night. Philadelphia: University of Pennsylvania Press; 1982.
269. Mignot E. Narcolepsy: pharmacology, pathophysiology, and genetics. In: Kryger M, Roth T, Dement W, eds. Principles and Practice of Sleep Medicine, 4th ed. Philadelphia: Elsevier Saunders; 2005:761–779.
270. Montplaisir J, Poirier G. HLA in disorders of excessive sleepiness without cataplexy in Canada. In: Honda Y, Juji T, eds. HLA in Narcolepsy. Berlin: Springer-Verlag; 1988:186–190.
271. Mitler M, Aldrich M, Koob G, et al. Narcolepsy and its treatment with stimulants: ASDA standards of practice. Sleep 1994;17:352–371.
272. Auger R, Goodman S, Silber M, Krahn L, Pankratz V, Slocum N. Risks of high-dose stimulants in the treatment of disorders of excessive somnolence: a case–control study. Sleep 2005; 28(6):667–672.
273. Black J, Hirshkowitz M. Modafinil for treatment of residual excessive sleepiness in nasal continuous positive airway pressure-treated obstructive sleep apnea/hypopnea syndrome. Sleep 2005;28(4):464–471.
274. US Xyrem in narcolepsy multi-center study group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep 2002;25:42–49.
275. Jacobson A, Kales J, Kales A. Clinical and electrophysiological correlates of sleep disorders in children. In: Kales A, ed. Sleep: Physiology and Pathology. Philadelphia: JB Lippincott; 1969:109–118.
276. Salzavulo P, Chevalier A. Sleep problems in children and their relationship with early disturbances of the waking-sleeping rhythms. Sleep 1983;6:47–51.
277. Simonds J, Parraga H. Prevalence of sleep disorders and sleep behaviors in children and adolescents. J Am Acad Child Adolesc Psychiatry 1982;21:383–388.
278. Bixler E, Kales A, Soldatos C, et al. Prevalence of sleep disorders in the Los 278. Angeles metropolitan area. Am J Psychiatry 1979;136:1257–1262.
279. Cirignotta F, Zucconi M, Mondini S, et al. Enuresis, sleepwalking and nightmares: an epidemiological survey in the republic of San Marino. In: Guilleminault C, Lugaresi E, eds. Sleep/Wake Disorders: Natural History, Epidemiology, and Long-Term Evolution. New York: Raven Press; 1983:237–241.
280. Hublin C, Kaprio J, Partinen M, et al. Prevalence and genetics of sleepwalking: a population-based twin study. Neurology 1997;48:177–181.
281. Ohayon M, Caulet M, Priest R. Violent behavior during sleep. J Clin Psychiatry 1997;58(8):369–376.
282. Schenck C, Mahowald M. A polysomnographically documented case of adult somnambulism with long-distance automobile driving and frequent nocturnal violence: parasomnia with continuing danger as a noninsane automatism? Sleep 1995;18(9):765–772.
283. Broughton R, Billings R, Cartwright R, et al. Homicidal somnambulism: a case report. Sleep 1994;17(3):253–264.
284. Cartwright R. Sleepwalking violence: a sleep disorder, a legal dilemma, and a psychological challenge. Am J Psychiatry 2004;161:1149–1158.
285. Schenck C. Paradox Lost, Midnight in the Battleground of Sleep and Dreams. Minneapolis, MN: Extreme-Nights, LLC; 2005.
286. Schenck C, Milner D, Hurwitz T, Bundlie S, Mahowald M. A polysomnographic and clinical report on sleep-related injury in 100 adult patients. Am J Psychiatry 1989;146(9):1166–1173.
287. Mahowald M, Schenck C. REM sleep parasomnias. In: Kryger M, Roth T, Dement W, eds. Principles and Practice of Sleep Medicine, 4th ed. Philadelphia: Elsevier Saunders; 2005: 897–916.
288. Schenck C. Sleep Runners: the stories behind everyday parasomnias. St. Paul, MN: Slow Wave Films, LLC; 2004.
289. Schenck C, Boyd J, Mahowald M. A parasomnia overlap disorder involving sleepwalking, sleep terrors, and REM sleep behavior disorder in 33 polysomnographically confirmed cases. Sleep 1997;20(11):972–981.
290. Schenck C, Hurwitz T, O'Connor K, Mahowald M. Additional categories of sleep-related eating disorders and the current status of treatment. Sleep 1993;16(5):457–466.
291. Vetrugno R, Manconi M, Ferini-Strambi L, Provini F, Plazzi G, Montagna P. Nocturnal eating: sleep-related eating disorder or night eating syndrome? A videopolysomnographic study. Sleep 2006;29(7):949–954.
292. Winkelman J. Sleep-related eating disorder and night eating syndrome: sleep disorders, eating disorders, or both? Sleep 2006;29(7):876–877.
293. Ebrahim I. Somnambulistic sexual behaviour (sexsomnia). J Clin Forensic Med 2006;13(4):219–224.
294. Shapiro C, Grajanovic N, Fedoroff J. Sexsomnia—a new parasomnia? Can J Psychiatry 2003;48(5):311–317.
295. Pressman M. Hypersynchronous delta sleep EEG activity and sudden arousals from slow-wave sleep in adults without a history of parasomnias: clinical and forensic implications. Sleep 2004;27(4):706–710.

296. Schenck C, Pareja J, Patterson A, Mahowald M. Analysis of polysomnographic events surrounding 252 slow-wave sleep arousals in thirty-eight adults with injurious sleepwalking and sleep terrors. J Clin Neurophysiol 1998;15(2): 159–166.
297. Zadra A, Pilon M, Joncas S, Rompre S, Montplaisir J. Analysis of postarousal EEG activity during somnambulistic episodes. J Sleep Res 2004;13(3):279–284.
298. Bassetti C, Vella S, Donati F, Wielepp P, Weder B. SPECT during sleepwalking. Lancet 2000;356:484–485.
299. Lapierre O, Montplaisir J. Polysomnographic features of REM sleep behavior disorder: development of a scoring method. Neurol 1992;42:1371–1374.
300. Consens F, Chervin R, Koeppe R, et al. Validation of a polysomnographic score for REM sleep behavior disorder. Sleep 2005;28(8):993–997.
301. Ferini-Strambi L, Di Gioia M, Castronovo V, Oldani A, Zucconi M, Cappa S. Neuropsychological assessment in idiopathic REM sleep behavior disorder (RBD). Does the idiopathic form of RBD really exist? Neurology 2004;62:41–45.
302. Schenck C, Bundlie S, Mahowald M. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder. Neurology 1996;46:388–393.
303. Schenck C, Bundlie S, Mahowald M. REM behavior disorder (RBD): delayed emergence of parkinsonism and/or dementia in 65% of older men initially diagnosed with idiopathic RBD, and analysis of the minimum and maximum tonic and/or phasic electromyographic abnormalities found during REM sleep. Sleep 2003;26(abstract suppl):A316.
304. Boeve B, Silber M, Parisi J, et al. Synucleinopathy pathology and REM sleep behavior disorder plus dementia or parkinsonism. Neurology 2003;61:40–45.
305. Fantini M, Ferini-Strambi L, Montplaisir J. Idiopathic REM sleep behavior disorder: toward a better nosologic definition. Neurology 2005;64:780–786.
306. Schenck C, Mahowald M. REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. Sleep 2002;25(2): 120–138.
307. Hefez A, Allodi F, Moldofsky H. Nightmares, sleep and symptoms in survivors of torture. Sleep Res 1985;14:129.
308. Husain A, Miller P, Carwile S. REM sleep; behavior disorder: potential relationship to post-traumatic stress disorder. J Clin Neurophysiol 2001;18(2):148–157.
309. Ohayon M, Guilleminault C, Priest R. Night terrors, sleepwalking, and confusional arousals in the general population: Their frequency and relationship to other sleep and mental disorders. J Clin Psychiatry 1999;60(4):268–276.
310. Boller F, Wright D, Cavalieri R, Mitsumoto H. Paroxysmal 'nightmares', sequel of a stroke responsive to diphenylhydantoin. Neurology 1975;25:1026–1028.
311. Cadhillac J. Complex partial seizures and REM sleep. In: Sterman M, Shouse M, Passouant P, eds. Sleep and Epilepsy. New York: Academic Press; 1982:315–324.
312. D'Cruz ON, Vaughn B. Nocturnal seizures mimic REM behavior disorder. Am J END Technol 1997;37:258–264.
313. Epstein A, Hill W. Ictal phenomena during sleep of a temporal lobe epileptic. Arch Neurol 1966;155:367–375.
314. Louden M, Morehead M, Schmidt H. Polyspikes in REM sleep mimicking REM sleep behavior disorder. Sleep Res 1994;23:283.
315. Mahowald M, Schenck C. Parasomnia purgatory: the epileptic/non-epileptic parasomnia interface. In: Gates J, Rowan A, eds. Non-epileptic seizures, 2nd ed. Boston, MA: Butterworth-Heinemann; 2000:71–94.
316. Silvestri R, DeDomenico P, Musolino R, et al. Nocturnal complex partial seizures precipitated by REM sleep. Eur Neurol 1989;29:80–85.
317. Maselli R, Rosenberg R, Spire J. Episodic nocturnal wanderings in non-epileptic young patients. Sleep 1988;11:156–161.
318. Pedley T, Guilleminault C. Episodic nocturnal wanderings responsive to anti-convulsant drug therapy. Ann Neurol 1977;2:30–35.
319. Lugaresi E, Cirignotta F. Hypnogenic paroxysmal dystonia: Epileptic seizure or a new syndrome? Sleep 1981;4(2): 129–138.
320. Lugaresi E, Cirignotta F, Montagna P. Nocturnal paroxysmal dystonia. J Neurol Neurosurg Psychiatry 1986;49:375–380.
321. Boeve B, Silber M, Ferman T, Lucas J, Parisi J. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. Mov Disord 2001;16:622–630.
322. Guilleminault C, Kirisoglu C, Bao G, Arias V, Chan A, Li K. Adult chronic sleepwalking and its treatment based on polysomnography. Brain 2005;128(5):1062–1069.
323. Guilleminault C, Sylvestri R. Disorders of arousal and epilepsy during sleep. In: Sterman M, Shouse M, Passouant P, eds. Sleep and Epilepsy. New York: Academic Press; 1982: 513–531.
324. Nalamalapu U, Goldberg R, DiPhillipo J, Fry J. Behaviors simulating REM behavior disorder in patients with severe obstructive sleep apnea. Sleep Res 1996;25:311.
325. Schenck C, Milner D, Hurwitz T, et al. Sleep-related injury in 85 adult patients: a polysomnographic study. Sleep Res 1988;17:247.
326. Thorpy M. Rhythmic movement disorder. In: Thorpy M, ed. Handbook of Sleep Disorders. New York: Marcel Dekker, Inc; 1990:609–629.
327. Whyte J, Kavey N, Gidro-Frank S. A self-destructive variant of jactatio captitis nocturna. J Nerv Ment Dis 1991;179(1):49–50.
328. Schenck C, Milner D, Hurwitz T, Bundlie S, Mahowald M. Dissociative disorders presenting as somnambulism: polysomnographic, video and clinical documentation (8 cases). Dissoc 1989;2(4):194–204.
329. Hauri P, Friedman M, Ravaris C. Sleep in patients with spontaneous panic attacks. Sleep 1989;12(4):323–337.
330. Mahowald M, Schenck C, Rosen G, Hurwitz T. The role of a sleep disorder center in evaluating sleep violence. Arch Neurol 1992;49:604–607.
331. Joncas S, Zadra A, Paquet J, Montplaisir J. The value of sleep deprivation as a diagnostic tool in adult sleepwalkers. Neurology 2002;58:936–940.
332. Kolivakis T, Margolese H, Beauclair L, Chouinard G. Olanzapine-induced somnambulism. Am J Psychiatry 2001; 158(7):1158.
333. Mahowald M, Cramer-Bornemann M. NREM sleep-arousal parasomnias. In: Kryger M, Roth T, Dement W, eds. Principles

and Practice of Sleep Medicine, 4th ed. Philadelphia: Elsevier Saunders; 2005:889–896.
334. Morgenthaler T, Silber M. Amnestic sleep-related eating disorder associated with zolpidem. Sleep Med 2002;3(4): 323–327.
335. Jouvet M, Delorme F. Locus coeruleus et sommeil paradoxal. C R Soc Biol 1965;159:895–899.
336. Albin R, Koeppe R, Chervin R, Consens F, Wernette K, Frey K. Decreased striatal dopaminergic innervation in REM sleep behavior disorder. Neurology 2000;55:1410–1412.
337. Eisensehr I, Linke R, Noachtar S, Scwarz J, Gildehaus F, Tatsch K. Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behaviour disorder—comparison with Parkinson's disease and controls. Brain 2000;123: 1155–1160.
338. Olson E, Boeve B, Silber M. Rapid eye movement sleep behavior disorder: demographic, clinical and laboratory findings in 93 cases. Brain 2000;123:331–339.
339. Mahowald M. Does "idiopathic REM sleep behavior disorder" exist? Sleep 2006;29(7):927–933.
340. Onofrj M, Luciano AL, Thomas A, Iacono D, D'Andreamatteo G. Mirtazapine induces REM sleep behavior disorder (RBD) in parkinsonism. Neurology 2003;60(1):113–115.
341. Louden MB, Morehead MA, Schmidt HS. Activation by selegiline (Eldepryle) of REM sleep behavior disorder in parkinsonism. WV Med J 1995;91(3):101.
342. Schenck CH, Mahowald MW, Kim SW, O'Connor KA, Hurwitz, TD. Prominent eye movements during NREM sleep and REM sleep behavior disorder associated with fluoxetine treatment of depression and obsessive–compulsive disorder. Sleep 1992;15(3):226–235.
343. Winkelman JW, James L. Serotonergic antidepressants are associated with REM sleep without atonia. Sleep 2004;27(2): 317–321.
344. Schenck CH, Mahowald MW. Polysomnographic, neurologic, psychiatric, and clinical outcome report on 70 consecutive cases with REM sleep behavior disorder (RBD): sustained clonazepam efficacy in 89.5% of 57 treated patients. Cleveland Clinic J Med 1990;57(suppl):9–23.
345. Schenck C, Mahowald M. Motor dyscontrol in narcolepsy: rapid-eye-movement (REM) sleep without atonia and REM sleep behavior disorder. Ann Neurol 1992;32(1):3–10.
346. Kohen D, Mahowald M, Rosen G. Sleep-terror disorder in children: the role of self-hypnosis in management. Am J Clin Hypn 1992;34(4):233–244.
347. Koe G. Hypnotic treatment of sleep terror disorder: a case report. Am J Clin Hypn 1989;32(1):36–40.
348. Hauri P, Silber M, Boeve B. Treating parasomnias with hypnosis [abstract]. Sleep 2004;27:A286.
349. Hurwitz T, Mahowald M, Schenck C, Schluter J, Bundlie S. A retrospective outcome study and review of hypnosis as treatment of adults with sleepwalking and sleep terror. J Nerv Ment Dis 1991;179(4):228–233.
350. Goldbloom D, Choinard G. Clonazepam in the treatment of neuroleptic-induced somnambulism. Am J Psychiatry 1984; 141:1486.
351. Schenck C, Mahowald M. Combined bupropion-levodopa-trazodone therapy of sleep-related eating and sleep disruption in two adults with chemical dependency. Sleep 2000;23(5): 587–588.
352. Winkelman J. Efficacy and tolerability of open-label topiramate in the treatment of sleep-related eating disorder: a retrospective case series. J Clin Psychiatry 2006;67:1729–1734.
353. Schenck C, Mahowald M. Topiramate therapy of sleep related eating disorder (SRED). Sleep 2006;29(suppl):A268.
354. Schenck C, Mahowald M. Polysomnographic, neurologic, psychiatric, and clinical outcome report on 70 consecutive cases with REM sleep behavior disorder (RBD): sustained clonazepam efficacy in 89.5% of 57 treated patients. Cleveland Clin J Med 1990;57(Suppl):9–23.
355. Schenck C, Mahowald M. Long-term, nightly benzodiazepine treatment of injurious parasomnias and other disorders of disrupted nocturnal sleep in 170 adults. Am J Med 1996;100:333–337.
356. Boeve B, Silber M, Ferman T. Melatonin therapy for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Med 2003;4:281–284.
357. Kunz D, Bes F. Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation. Mov Disord 1999;14(3):507–511.
358. Takeuchi N, Uchimura N, Hashizume Y, et al. Melatonin therapy for REM sleep behavior disorder. Psychiatry Clin Neurosci 2001;55(3):267–269.
359. Ringman J, Simmons J. Treatment of REM sleep behavior disorder with donepezil: a report of three cases. Neurol 2000;55(6):870–871.
360. Fantini M, Gagnon J, Filipini D, Montplaisir J. The effects of pramipexole in REM sleep behavior disorder. Neurol 2003;61(10):1418–1420.
361. Schmidt M, Koshal V, Schmidt H. Use of pramipexole in REM sleep behavior disorder: results from a case series. Sleep Med 2006;7(5):418–423.
362. Gagnon J, Postuma R, Montplaisir J. Update on the pharmacology of REM sleep behavior disorder. Neurol 2006;67(5):742–747.
363. Krakow B, Kellner R, Pathak D, Lambert L. Imagery rehearsal treatment for chronic nightmares. Behav Res Ther 1995;33(7):837–843.
364. Krakow B, Zadra A. Clinical management of chronic nightmares: imagery rehearsal therapy. Behav Sleep Med 2006;4(1):45–70.
365. Brophy M. Cyproheptadine for combat nightmares in posttraumatic stress disorder and dream anxiety disorder. Mil Med 1991;156(2):100–101.
366. Gupta S, Popli A, Bathurst E, Hennig L, Droney T, Keller P. Efficacy of cyproheptadine for nightmares associated with posttraumatic stress disorder. Compr Psychiatry 1998;39(3): 160–164.
367. Harsh H. Cyproheptadine for recurrent nightmares. Am J Psychiatry 1986;143(11):1491–1492.
368. Rijnders R, Laman D, van Diujn H. Cyproheptadine for posttraumatic nightmares. Am J Psychiatry 2000;157(9):1524–1525.
369. Clark R, Canive J, Calais L, Qualls C, Brugger R, Vosburgh R. Cyproheptadine treatment of nightmares associated with posttraumatic stress disorder. J Clin Psychopharm 1999;19(5): 486–487.
370. Peskind E, Bonner L, Hoff D, Raskind M. Prazosin reduces trauma-related nightmares in older men with chronic

posttraumatic stress disorder. J Geriatr Psychiatry Neurol 2003;16(3):165–171.
371. Daly C, Doyle M, Radkind M, Raskind E, Daniels C. Clinical case series: the use of prazosin for combat-related recurrent nightmares among operation Iraqi Freedom combat veterans. Mil Med 2005;170(6):513–515.
372. Raskind M, Peskind E, Kanter E, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry 2003;160:371–373.
373. Raskind M, Thompson C, Petrie E, et al. Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. J Clin Psychiatry 2002;63:565–568.
374. Taylor F, Raskind M. The alpha1-adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. J Clin Psychopharm 2002;22(1):82–85.
375. Raskind M, Peskind E, Hoff D, et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with posttraumatic stress disorder. Biol Psychiatry 2007;61(8):928–934.
376. Horrigan J, Barnhill L. The suppression of nightmares with guanfacine. J Clin Psychiatry 1996;57(8):371.
377. Kinzie J, Sack R, Riley C. The polysomnographic effects of clonidine on sleep disorders in posttraumatic stress disorder: a pilot study with Cambodian patients. J Nerv Ment Dis 1994;182(10):585–587.
378. Iber C, Ancoli-Israel S, Chesson A, and Quan SF for the American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, 1st ed.: Westchester, Illinois: American Academy of Sleep Medicine, 2007.
379. Stefansson H, Rye DB, Hicks A, et al. A Genetic Risk Factor for Periodic Limb Movements in Sleep. NEJM 2007;357: 1–9.
380. Collop NA, Anderson WM, Boehlecke B, et al. Clinical Guidelines for the Usde of Unattended Portable Monitors in the Diagnosis of Obstructive Sleep Apnea in Adult Patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med 2007;3(7):737–747.
381. Schenck CH, Arnulf I, Mahowald MW: Sleep and Sex: What Can Go Wrong? A Review of the Literature on Sleep Related Disorders and Abnormal Sexual Behaviors and Experiences. Sleep 2007;30(6):683–702.